**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 66125

**Manuscript Type:** REVIEW

**Gastric cancer: an epigenetic view**

Tang SY *et al*. Epigenetics for gastric cancer

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**Author contributions:** Deng GT, Zeng FR, and Tang SY designed the study; Tang SY and Zeng FR wrote the manuscript; Zhou PJ and Meng Y revised the manuscript; All the authors supported the study.

**Supported by** the fellowship of the China Postdoctoral Science Foundation, No. 2020M682594.

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**Received:** March 21, 2021

**Revised:** May 17, 2021

**Accepted:** **December 21, 2021**

**Published online:**

**Abstract**

Gastric cancer (GC) poses a serious threat worldwide with unfavorable prognosis mainly due to late diagnosis and limited therapies. Therefore, precise molecular classification and search for potential targets are required for diagnosis and treatment, as GC is complicated and heterogeneous in nature. Accumulating evidence indicates that epigenetics plays a vital role in gastric carcinogenesis and progression, including histone modifications, DNA methylation and non-coding RNAs. Epigenetic biomarkers and drugs are currently under intensive evaluations to ensure efficient clinical utility in GC. In this review, key epigenetic alterations and related functions and mechanisms are summarized in GC. We focus on integration of existing epigenetic findings in GC for the bench-to-bedside translation of some pivotal epigenetic alterations into clinical practice and also describe the vacant field waiting for investigation.

**Key Words:** Gastric cancer; Epigenetics; Histone modifications; DNA methylation; Non-coding RNAs

Tang SY, Zhou PJ, Meng Y, Zeng FR, Deng GT. Gastric cancer: An epigenetic view. *World J Gastrointest Oncol* 2021; In press

**Core Tip:** Epigenetics plays a vital role in gastric carcinogenesis and progression. In this review, key epigenetic alterations and related functions and mechanisms are summarized in gastric cancer.

**INTRODUCTION**

Gastric cancer (GC) is one of the most common malignant tumors of the digestive tract and ranks as the fifth leading cause of morbidity and second leading cause of mortality worldwide, posing a serious threat to all human beings[1]. Residents in South and East of Asia including China, Japan and Korea are reported to have a higher risk of GC[2]. Due to the unconspicuous symptoms in the early stage of GC, many patients are first diagnosed as advanced GC accompanied by tumor infiltration and metastasis. Despite of combined treatment of surgery, chemotherapy, radiotherapy, and sometimes targeted therapy and immunotherapy, GC still shows a poor prognosis with the 5-year overall survival less than 30%[3,4]. Currently routine screening for GC is endoscopy and histological examination, which is costly, invasive and often painful to patients. Therefore, development of new or alternative methods for screening, diagnosis and treatment to GC is of great clinical significance.

Epigenetics has been illustrated to be associated with the diagnosis and treatment of GC patients. GC is highly complicated and heterogeneous in nature and often genetically divided into familial and sporadic disease. Familial GC, constituting about 10% of GC patients, has a close connection to genetic alterations[5]. Sporadic GC (90% of GC) is largely related to *helicobacter pylori* (*H. pylori*) infection and evolves in a canonical model of chronic inflammation, atrophy, intestinal metaplasia, dysplasia and finally adenocarcinoma, which is characterized by typically epigenetic alterations but scarce genetic changes across over the stages[6]. With rapid progress in epigenomics, precise molecular classification towards GC seems admirable in research and clinical medicine. In 2014, The Cancer Genome Atlas identified GC into four molecular subtypes including Epstein–Barr virus (EBV) associated, microsatellite instable (MSI), chromosomal instability (CIN), and genomically stable (GS)[7]. Apparently, GS means the genome is stable in this type of GC[8]. Among the four classes, MSI patients have the best overall prognosis and the lowest frequency of recurrence with high incidence of gene mutations and DNA methylation. Patients in EBV-subtype are associated with Epstein-Barr virus infection and have extremely high DNA methylation status. In the patients with CIN subtype, the largest proportion of GC, is more prone to chromosomal diseases such as chromosome rearrangement and aberration. Radically distinct clinical outcomes are presented in different subtypes.

In this review, we mainly explore GC from an epigenetic view and summarize key epigenetic alterations and related functions and mechanisms, with special attention to histone modifications and the translational findings which guide us towards better clinical utility.

**HISTONE MODIFICATIONS**

Nucleosome, as a major unit of chromatin, consists of wrapped DNA and a histone octamer formed by two copies of H2A, H2B, H3 and H4 proteins[9]. Each histone contains an accessible amino terminal tail rich in lysine, arginine, serine and threonine residues, which is often modified post-translationally and the process is called posttranslational modifications (PTMs). Studies have shown that histone PTMs in GC mainly including acetylation, methylation, phosphorylation and ubiquitination are involved in various pathophysiological cellular functions such as carcinogenesis, inflammation and epithelial-mesenchymal transition (Figure 1)[10]. In recent years, some new modifications, such as succinylation, sumoylation, butyrylation and crotonylation, have been discovered in the occurrence and progression of other gastrointestinal tumors, such as esophageal, colorectal, and hepatocarcinoma liver cancer[11-14], which provide new insights in functions and mechanisms and even therapeutic potential for cancer diagnosis and treatments. Notably, those new types of histone modifications remain a vacant field in GC and thereby it may be an innovative and interesting field to explore in the near future.

***Histone acetylation***

As the most common form of PTMs in GC, acetylation always occurs in N-terminal lysine residues of histone H3 and H4 and is associated with chromatin remodeling, regulation of transcription, translation and DNA repair. The acetylation of histones catalyzed by histone acetylase (HATs) transfers acetyl moieties from coenzyme A to lysine residues, opens the chromatin structure and makes it accessible to transcriptional factors, thus activating gene transcription. Instead, the histone deacetylase (HDACs) removes the acetyl groups from histone and results in repression of transcription. HATs consist of three families including GCN5, MYST and p300/CBP, while HDACs contain four classes including type I (HDAC 1,2,3,8), type II (HDAC 4,7,9,10), type III (SIRT 1-7) and type IV (HDAC 11)[15,16]. The reversible acetylation and deacetylation processes mainly facilitate GC progression by activating oncogene expression and silencing tumor suppressor gene expression.

Studies revealed that high H3K9Ac positive cells were associated with undifferentiated GC, suggesting poor prognosis of GC[17]. Further, BMP8B was highly expressed in GC tissues other than adjacent normal tissues, and reduced acetylation level of BMP8B loci on H3K9 and H4K16 influenced the development of poorly differentiated gastric tumors[18]. Many genes encoding HATs, such as KAT2B and EP300, are often genetically depleted or mutated in GC, and are significantly correlated with TNM staging[19,20]. IFN-γ-induced upregulation of histone H3 Lysine 9 acetylation (H3K9) level in gene promoter accelerates the expression of B7-H1, which contributes to tumor immune evasion in HGC-27 cells[21]. Wisnieski *et al*[22] demonstrated hypoacetylation of histone H3 in the initiator domain of CDKN1A decreased its mRNA level and reduced antitumor effect in GC. Besides, *H. pylori*-infection inhibited recruitment of HAT p300 to the p27 promoter which caused the hypoacetylation status in histone H4, then induced the downregulated p27 mRNA expression, and finally led to gastric carcinogenesis[23].

***Histone methylation***

Histone methylation usually takes place on H3 and H4 Lysine or arginine residues, catalyzed by histone methyltransferases (HMTs) and reversely controlled by histone demethylases (HDMs). The methylation could be single or multiple methylations to form mono-methylation (me1), di-methylation (me2) and tri-methylation (me3), participating in the formation and maintenance of chromatin structure, DNA repair, gene inactivation and transcription[24]. Methylations on different sites have different functions in regulation of gene expression. In general, methylation of arginine residues, methylation of lysine H3K4 and H3K36, and monomethylation of H3K27 are associated with gene activation, while methylation of H3K9, H3K79 and H4K20, and dimethylation and trimethylation of H3K27 might cause gene silencing[25,26].

Specifically, repression of HDMs KDM5A and DPY300 subunits upregulated H3K4me level, inhibiting GC cell proliferation[27]. However, overexpression of HDMs LSD1 declined methylation of H3K4 in p21 promoter and repressed the transcription of p21, resulting in progression of GC[28]. An assay of familial GC patients identified INSR, FBXO24 and DOT1L as new susceptibility genes in diffuse gastric carcinoma, in which DOT1L was a histone methyltransferase involved in the mono, di and tri-methylation of H3K79, suggesting the contributing role of H3K79 in gastric carcinogenesis[29]. Methylation of H3K27 is well-investigated in GC. A paired-study of 117 GC patients showed that the level of H3K27me3 in GC and normal tissue was 56.4% and 7.25%, respectively, which negatively correlated with GC overall survival[30]. Besides, knockdown of demethylases SETDB2 was found to accelerate the expression of tumor suppressor genes WWOX and CADM1, and significantly reduced cell growth, migration and invasion in GC cells[31].

***Histone phosphorylation***

Histone phosphorylation is a dynamical process mediated by histone kinases and phosphatases, in which the phosphate group is transferred from ATP to the histone serine and threonine residues. There are several accessible sites in histone phosphorylation including H1.4 Ser27, H2AX Ser139 ( also called γ-H2AX), H3 Ser10, H3 The3 and H4 Ser1[32,33]. Particularly, histone H3 is phosphorylated at Ser10 during mitosis in all eukaryotes and induction of phosphorylation in interphase has been shown to correlate with chromosome condensation prior to mitosis[34]. Histone phosphorylation functions as a switch on chromosomal folding, compression, segregation, transcriptional regulation, cell signal transduction, cell apoptosis, and DNA damage repair[35,36].

Histone phosphorylation frequently happens in H3 and H4 with a dual role in cancer progression[32,33]. For instance, phosphorylated histone H3 at position of serine10 (H3S10) by MSK1 promoted cell proliferation during gastric tumorigenesis *via* the activation of downstream transcriptional factor NFATc2-related inflammatory pathway[37]. H3S10 phosphorylation also played a vital prognostic role in defining negative resection margins in GC due to its lower expression in the surgical resection margins[38]. A cohort of 122 GC patients further indicated phosphorylated histone H3 overexpression could be an independent prognostic factor[39]. Moreover, repression of Aurora B - mediated H1.4 phosphorylation at Ser27, caused by Ras - ERK1/2 signaling, evidently participated in the progression of GC[40].

***Histone ubiquitination***

Unlike the three types of histone modifications described above, histone ubiquitination always works in the crosstalk with other modifications. Histone ubiquitination often acts subsequently after histone acetylation and methylation or modifies the stability and the activity of enzymes in these acetylation and methylation processes, which endures a synergic effect on cell division, cell cycle, DNA damage and cell apoptosis in GC[41]. When the histone, usually H2A and H2B, binds to one or several ubiquitins on lysine residues, it is called mono- or poly- ubiquitination and tends to work in the following three ways: alterations of chromosome structure, recruitment and activation of downstream proteins, and degradation in proteasome pathway[42]. Ubiquitination is a reversible process in which ubiquitin is removed from polypeptides by deubiquitinases (DUBs), a superfamily of cysteine proteases and metalloproteases that cleave ubiquitin-protein bonds[43,44].

Hahn *et al*[45] identified that ring finger proteins RNF20 and RNF40 constituted a heterodimeric complex that functions as the E3 ubiquitin ligase for monoubiquitination of histone H2B at lysine 120 (H2B-K120) and the tumor suppressor CDC73 exerted antitumor effect in GC through the maintenance of H2B-K120 monoubiquitination. Besides, histone ubiquitination presents a therapeutic potential in GC as the expression of ubiquitinated-H2B was significantly lower in the malignant tissues and different differentiated tumors had variant levels of H2B ubiquitination[46].

**DNA METHYLATION**

In contrast to histone methylation,DNA methylation is a more frequent and comprehensive epigenetic modification (Figure 2), mediated by DNA methyltransferase (DNMTs) and demethylases. It refers to the transfer of the methyl group (CH3) from S.adenosylmethionine to C5 and forms 5-methylcytosine[47,48]. DNA methylation occurs in the dinucleotide CpG sequence, which may form CpG islands and dispersed sequences. CpG islands exist in around 60%-70% of gene promoters in human and consist of CpG core and shore area[49]. CpG core has a specific inhibitory effect on methylation, while the shore area, also known as transitional CpG region, is variable sites for dynamical alterations between hypomethylated and hypermethylated groups. In normal cells, CpG islands are non-methylated and other CpG sequence are methylated. Once stimulated by intrinsic or extrinsic factors, the methylation status changed and caused alterations in gene transcription, and consequently lead to tumorigenesis[48].

Aberrant DNA hypermethylation usually happens in the promoter of tumor suppressor genes in GC like p16, RASSF1A and hMLH1. Hypermethylation inhibits gene transcription by reducing binding to transcription factors, thereby impeding DNA readability and resulting in gene silencing[50]. Specifically, alteration of methylation in p16 promoter inhibited the cell cycle in G1 phase and induced 5-fluorurazil chemo-resistance in GC[51]. Abnormal methylation of RASSF1A gene promoter reduced RASSF1A expression, decreased cyclin D1 accumulation, and arrested cell cycle. Consistently, GC patients presented evidently higher frequency of aberrant methylation in RASSF1A promoter than control group, indicating the potential of methylated RASSF1A promoter as a molecular marker for the diagnosis of GC[52]. In addition to methylation alterations in promoter, hypomethylation at gene body regions has a distinct association with transcription and gene hypomethylation also exerts profound effects on cancer progression[53]. For instance, hypomethylation of SAT-α and L1 was associated with shortened survival in advanced GC patients[54]. And Lineage-specific RUNX3 hypomethylation constituted the immune component in GC and was associated with the early inflammatory, preneoplastic and tumor stages[55]. Genome-wide methylation sequencing studies in GC identified both hypo- and hyper-methylation events across the genome, suggesting a dual role of global genomic methylation in the stages of gastric carcinogenesis[56].

*H. pylori*-induced DNA Methylation is a hot research area in the development of GC. Numerous researches revealed that *H. pylori*, classified as Class I carcinogen by WHO, induced and accumulated aberrant DNA methylation through continuous chronic inflammation in gastric mucosae, and such high level of epigenetic field defects increased the risk of gastric carcinogenesis[57]. For example, *H. pylori* infection upregulated inflammatory response genes like IL-1β, Nos2, and Tnf, and promoted the infiltration of monocytes/macrophages with residual neutrophils in noncancerous mucosae, which induced a large number of aberrant DNA methylation in tumor suppressor genes and led to malignant transformation[58]. Eradication of *H. pylori* had subtle influence on the decrease of DNA methylation in gerbils, while application of immunosuppressive agent (*e.g.,* cyclosporin A) and demethylation agent (*e.g.,* 5-Aza-2-deoxycytidine) could evidently reduce level of DNA methylation and prevent development of GC[59,60]. Moreover, high levels of DNA methylation were found in gastric biopsies of inflammatory and precancerous lesions, comparing to adjacent normal tissue, and were also correlated with a greater risk of GC incidence[61]. *H. pylori*-induced DNA methylation takes place in various genes involved in cell adhesion, cell cycle, DNA damage repair, inflammation, and autophagy, which allows intensive interfered targets of such epigenetic defects in diagnostic biomarker and cancer prevention[58,62].

**NON-CODING RNAS**

Non-coding RNAs consist of microRNAs (miRNAs), long non coding RNAs (lncRNAs), circular RNAs (circRNAs), small nucleolar RNAs (snoRNAs), small interfering RNAs (siRNAs), *etc*.[63]. Since the first two non-coding RNA lineage defective 4 (lin-4)[64] and lethal 7 (let-7)[65] were identified in 1993 and 2000, researchers realized that in addition to protein, some RNAs lacking of protein-coding regions, which are called non-coding RNAs, were still conserved functional molecules and required for many biological processes. Among non-coding RNAs, miRNAs, lncRNAs and circRNAs were found to have plenty of functions in GC (Figure 3), including cell proliferation, cell cycle arrest, apoptosis, migration, invasion and chemo- or radio-sensitivity[66,67].

***miRNAs***

MicroRNAs are a class of small RNAs with 18-24 nucleotides and they repress translation process and silence target gene through complementary binding with 3’untranslated terminal region (UTR) of mRNA[68]. A shaped understanding towards miRNAs has been established in the past two decades due to numerous miRNAs arrays conducted in GC. Taking the largest scale of GC miRNAs array cohort for example, a general miRNAs signature profiling was developed, in which 22 oncogenic miRNAs and 13 tumor suppressor miRNAs were identified in 353 primary Japanese gastric tumor samples. In this study, authors also revealed that different histological subtypes had different miRNA signatures[69] as diffuse-type showed 2 folds of proportion in upregulated miRNAs to intestinal-type GC. Specifically, low expression of let-7g and miR-433 and high expression of miR-214 were associated with unfavorable outcomes in GC patients[69]. MiRNAs have an edge on GC diagnosis potential over other epigenetic factors because they alter quickly and are easy to be detected in the early stage of GC. Yu *et al*[70] performed a miRNAs microarray in early GC mouse model and the result showed that miR200-family promoted the initiation of GC and the integration of miR200-family’s 15 target gene would provide superior predictive sensitivity and specificity for overall survival compared with each early GC indicator alone. Here we summarized the up- or down-regulated miRNAs in GC (Table 1).

***LncRNAs***

LncRNAs are longer than 200 nucleotides and exert profound influences on multiple biological functions through regulating transcription, chromatin remodeling and post-transcriptional process[71]. They work mainly in three ways: (1) interact with mRNA, control transcription and regulate cellular signaling pathways; (2) act as regulators of splicing and mRNA decay; (3) work as molecular decoys for miRNAs; and (4) interact with chromatin-modifying complexes or being a scaffold to maintain the structure of nuclear speckles[72-74]. Numerous lncRNAs have been uncovered the role and related mechanisms in GC. HOTAIR is a well-studied lncRNA and it is frequently overexpressed in GC, which may play a part in metastasis through following pathways: (1) being a sponge of miR-330[75] and miR-331-3p[76] to upregulate the downstream targets; (2) directly silencing HOXD[76] or miR34a expression[77]; (3) regulating Wnt/β-catenin and PI3K/Akt pathways[77]; and (4) inducing ubiquitination of Runx3[78]. Therefore, HOTAIR was considered to be a potent diagnostic and prognostic biomarker in GC. Most of lncRNAs in GC were found to be oncogenic, like H19, MNX1-AS1, MALAT1, HULC, UCA1, *etc.* However, some lncRNAs like CRNDE were identified to inhibit GC progression. Here we summarized the up- or down-regulated lncRNAs and the related targets and functions in GC (Table 2).

***CircRNAs***

CircRNAs are a novel class of conserved single-stranded RNA molecules derived from exonic or intronic sequences by precursor mRNA back-splicing[79]. Compared to linear RNAs, the circular structure of circRNAs confers enhanced stability to exonuclease digestion[80]. Partially similar to lncRNAs, circRNAs could also act as miRNAs sponge, regulators of alternative splicing and tools of sequestering functional proteins in gene expression and posttranscriptional modification[81]. However, some circRNAs were identified to encode functional proteins[82]. CircRNAs were reported to exert influences on tumor growth, therapeutic resistance, recurrence and metastasis[83]. GC-related sequencing data revealed a variety of circRNAs with pro- or anti-tumor roles, including CircPVT1, CircRNA\_001569, CircHIPK3, *etc.* CiRS-7, one of the mostly investigated circRNAs, is a sponge of miR-7. MiR-7 was known as a tumor suppressor miRNA, while ciRS-7 was found to act in an oncogenic role by antagonizing miR-7-mediated PTEN/PI3K/AKT pathway in GC. Overexpression of ciRS-7 accelerated the progression of GC[84]. Undoubtedly, circRNAs are of great value in research and are emerging as a rising star in the field of cancer biology and therapy. We listed some important circRNAs, as well as their targets and functions in Table 3.

**TRANSLATIONAL APPLICATION OF EPIGENETICS**

Researches on epigenetics not only revealed the underlying mechanism of cancer initiation and progression, but also provided novel diagnostic and prognostic candidate biomarkers and therapeutic targets. To the best of our knowledge, biomarkers in GC ranges from pivotal proteins, non-coding RNAs to plenty of modifications with various specificity and sensitivity, as well as epigenetic liquid biopsy, some of which have already shown favorable clinical utility (Table 4). Liquid biopsy is a simple, fast and non-invasive alternative to surgical biopsies, as blood or body fluid sample is always easy to collect. A sum of circulating tumor cells (CTCs) and cell-free nucleic acids (cfNAs) including DNA, mRNA and microRNAs could be detected in patient blood or body fluid[85]. Available information obtained from liquid biopsy could help doctors with cancer diagnosis and evaluation of clinical outcomes. Up to now, most of epigenetic liquid biopsies in GC were aberrant DNA methylations such as 5-methylcytosine (5mC), 5-hydroxymethylcytosine (5hmC), CD40 and GHSR hypermethylation and they even could be used to identify specific cancer types[86-88]. Moreover, CTCs were often detected based on miRNA or mRNA PCR assay due to its low concentration in blood.

From the therapeutic perspective, targets involved in epigenetic modifications are potential drug targets and they are mainly divided into two groups including enzymes in histone acetylation (HAT or HDAC) and methylation (DNMT or DMT), and non-coding RNAs (miRNA or lncRNA). Some epigenetic drugs have been approved by FDA such as HDAC inhibitors (SAHA) in treatment of cutaneous T-cell lymphoma and DNMT inhibitors (vidaza, decitabine) in treatment of myelodysplatic syndromes[2]. However, most of epigenetic drugs are undergoing clinical or preclinical tests and none of them were currently ready for clinical utility in GC. As the rapid development of GC epigenetics research in recent decades, it is of great significance to integrate existing findings to ensure efficient translation applications (Table 5).

**CONCLUSION**

Accumulating evidence revealed the critical role of epigenetic alterations in cancer initiation and progression. Herein, we comprehensively discussed the functions and mechanisms of epigenetic factors in GC. Drugs targeted HAT, HDAC, DNMT are undergoing preclinical and clinical trials, which is promising for improving the efficacy and survival to GC. However, epigenetic studies in GC are still challenged by lack of innovative findings in new types of histone modifications. Succinylation and sumoylation, for instance, have already been reported to participate in tumorigenesis and progression in other gastrointestinal cancers including esophageal, colorectal and liver cancer. We believe combined technologies like single cell sequencing and multiple protein omics sequencing will further broaden epigenetic investigation in gastric malignancy and GC patients will benefit from numerous epigenetic drugs in the future.

**REFERENCES**

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Theuer CP**, Kurosaki T, Ziogas A, Butler J, Anton-Culver H. Asian patients with gastric carcinoma in the United States exhibit unique clinical features and superior overall and cancer specific survival rates. *Cancer* 2000; **89**: 1883-1892 [PMID: 11064344 DOI: 10.1002/1097-0142(20001101)89:9<1883::aid-cncr3>3.3.co;2-8]

3 **Jin H**, Pinheiro PS, Callahan KE, Altekruse SF. Examining the gastric cancer survival gap between Asians and whites in the United States. *Gastric Cancer* 2017; **20**: 573-582 [PMID: 27866287 DOI: 10.1007/s10120-016-0667-4]

4 **Cheong JH**, Yang HK, Kim H, Kim WH, Kim YW, Kook MC, Park YK, Kim HH, Lee HS, Lee KH, Gu MJ, Kim HY, Lee J, Choi SH, Hong S, Kim JW, Choi YY, Hyung WJ, Jang E, Kim H, Huh YM, Noh SH. Predictive test for chemotherapy response in resectable gastric cancer: a multi-cohort, retrospective analysis. *Lancet Oncol* 2018; **19**: 629-638 [PMID: 29567071 DOI: 10.1016/S1470-2045(18)30108-6]

5 **Vogelaar IP**, van der Post RS, Bisseling TM, van Krieken JHJ, Ligtenberg MJ, Hoogerbrugge N. Familial gastric cancer: detection of a hereditary cause helps to understand its etiology. *Hered Cancer Clin Pract* 2012; **10**: 18 [PMID: 23231819 DOI: 10.1186/1897-4287-10-18]

6 **Tan P**, Yeoh KG. Genetics and Molecular Pathogenesis of Gastric Adenocarcinoma. *Gastroenterology* 2015; **149**: 1153-1162.e3 [PMID: 26073375 DOI: 10.1053/j.gastro.2015.05.059]

7 **Cristescu R**, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, Liu J, Yue YG, Wang J, Yu K, Ye XS, Do IG, Liu S, Gong L, Fu J, Jin JG, Choi MG, Sohn TS, Lee JH, Bae JM, Kim ST, Park SH, Sohn I, Jung SH, Tan P, Chen R, Hardwick J, Kang WK, Ayers M, Hongyue D, Reinhard C, Loboda A, Kim S, Aggarwal A. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 2015; **21**: 449-456 [PMID: 25894828 DOI: 10.1038/nm.3850]

8 **Cancer Genome Atlas Research Network.** Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]

9 **Kornberg RD**. Chromatin structure: a repeating unit of histones and DNA. *Science* 1974; **184**: 868-871 [PMID: 4825889 DOI: 10.1126/science.184.4139.868]

10 **Calcagno DQ**, Wisnieski F, Mota ERDS, Maia de Sousa SB, Costa da Silva JM, Leal MF, Gigek CO, Santos LC, Rasmussen LT, Assumpção PP, Burbano RR, Smith MA. Role of histone acetylation in gastric cancer: implications of dietetic compounds and clinical perspectives. *Epigenomics* 2019; **11**: 349-362 [PMID: 30672330 DOI: 10.2217/epi-2018-0081]

11 **Yang G**, Yuan Y, Yuan H, Wang J, Yun H, Geng Y, Zhao M, Li L, Weng Y, Liu Z, Feng J, Bu Y, Liu L, Wang B, Zhang X. Histone acetyltransferase 1 is a succinyltransferase for histones and non-histones and promotes tumorigenesis. *EMBO Rep* 2021; **22**: e50967 [PMID: 33372411 DOI: 10.15252/embr.202050967]

12 **Du L**, Fakih MG, Rosen ST, Chen Y. SUMOylation of E2F1 Regulates Expression of EZH2. *Cancer Res* 2020; **80**: 4212-4223 [PMID: 32816857 DOI: 10.1158/0008-5472.CAN-20-1259]

13 **Kishore C**. Epigenetic regulation and promising therapies in colorectal cancer. *Curr Mol Pharmacol* 2021 [PMID: 33573584 DOI: 10.2174/1874467214666210126105345]

14 **Wan J**, Liu H, Ming L. Lysine crotonylation is involved in hepatocellular carcinoma progression. *Biomed Pharmacother* 2019; **111**: 976-982 [PMID: 30841477 DOI: 10.1016/j.biopha.2018.12.148]

15 **Jenke R**, Reßing N, Hansen FK, Aigner A, Büch T. Anticancer Therapy with HDAC Inhibitors: Mechanism-Based Combination Strategies and Future Perspectives. *Cancers (Basel)* 2021; **13** [PMID: 33562653 DOI: 10.3390/cancers13040634]

16 **Saha S**. Histone Modifications and Other Facets of Epigenetic Regulation in Trypanosomatids: Leaving Their Mark. *mBio* 2020; **11** [PMID: 32873754 DOI: 10.1128/mBio.01079-20]

17 **Park YS**, Jin MY, Kim YJ, Yook JH, Kim BS, Jang SJ. The global histone modification pattern correlates with cancer recurrence and overall survival in gastric adenocarcinoma. *Ann Surg Oncol* 2008; **15**: 1968-1976 [PMID: 18470569 DOI: 10.1245/s10434-008-9927-9]

18 **Wisnieski F**, Leal MF, Calcagno DQ, Santos LC, Gigek CO, Chen ES, Artigiani R, Demachki S, Assumpção PP, Lourenço LG, Burbano RR, Smith MC. BMP8B Is a Tumor Suppressor Gene Regulated by Histone Acetylation in Gastric Cancer. *J Cell Biochem* 2017; **118**: 869-877 [PMID: 27748538 DOI: 10.1002/jcb.25766]

19 **Wisnieski F**, Calcagno DQ, Leal MF, Chen ES, Gigek CO, Santos LC, Pontes TB, Rasmussen LT, Payão SL, Assumpção PP, Lourenço LG, Demachki S, Artigiani R, Burbano RR, Smith MC. Differential expression of histone deacetylase and acetyltransferase genes in gastric cancer and their modulation by trichostatin A. *Tumour Biol* 2014; **35**: 6373-6381 [PMID: 24668547 DOI: 10.1007/s13277-014-1841-0]

20 **Kim MS**, Lee SH, Yoo NJ, Lee SH. Frameshift mutations of tumor suppressor gene EP300 in gastric and colorectal cancers with high microsatellite instability. *Hum Pathol* 2013; **44**: 2064-2070 [PMID: 23759652 DOI: 10.1016/j.humpath.2012.11.027]

21 **Deng R**, Zhang P, Liu W, Zeng X, Ma X, Shi L, Wang T, Yin Y, Chang W, Zhang P, Wang G, Tao K. HDAC is indispensable for IFN-γ-induced B7-H1 expression in gastric cancer. *Clin Epigenetics* 2018; **10**: 153 [PMID: 30537988 DOI: 10.1186/s13148-018-0589-6]

22 **Wisnieski F**, Calcagno DQ, Leal MF, Santos LC, Gigek CO, Chen ES, Demachki S, Artigiani R, Assumpção PP, Lourenço LG, Burbano RR, Smith MC. CDKN1A histone acetylation and gene expression relationship in gastric adenocarcinomas. *Clin Exp Med* 2017; **17**: 121-129 [PMID: 26567008 DOI: 10.1007/s10238-015-0400-3]

23 **Byun SW**, Chang YJ, Chung IS, Moss SF, Kim SS. Helicobacter pylori decreases p27 expression through the delta opioid receptor-mediated inhibition of histone acetylation within the p27 promoter. *Cancer Lett* 2012; **326**: 96-104 [PMID: 22867947 DOI: 10.1016/j.canlet.2012.07.032]

24 **Michalak EM**, Burr ML, Bannister AJ, Dawson MA. The roles of DNA, RNA and histone methylation in ageing and cancer. *Nat Rev Mol Cell Biol* 2019; **20**: 573-589 [PMID: 31270442 DOI: 10.1038/s41580-019-0143-1]

25 **Song Y**, Wu F, Wu J. Targeting histone methylation for cancer therapy: enzymes, inhibitors, biological activity and perspectives. *J Hematol Oncol* 2016; **9**: 49 [PMID: 27316347 DOI: 10.1186/s13045-016-0279-9]

26 **Jarrold J**, Davies CC. PRMTs and Arginine Methylation: Cancer's Best-Kept Secret? *Trends Mol Med* 2019; **25**: 993-1009 [PMID: 31230909 DOI: 10.1016/j.molmed.2019.05.007]

27 **Torres IO**, Kuchenbecker KM, Nnadi CI, Fletterick RJ, Kelly MJ, Fujimori DG. Histone demethylase KDM5A is regulated by its reader domain through a positive-feedback mechanism. *Nat Commun* 2015; **6**: 6204 [PMID: 25686748 DOI: 10.1038/ncomms7204]

28 **Liu YW**, Xia R, Lu K, Xie M, Yang F, Sun M, De W, Wang C, Ji G. LincRNAFEZF1-AS1 represses p21 expression to promote gastric cancer proliferation through LSD1-Mediated H3K4me2 demethylation. *Mol Cancer* 2017; **16**: 39 [PMID: 28209170 DOI: 10.1186/s12943-017-0588-9]

29 **Donner I**, Kiviluoto T, Ristimäki A, Aaltonen LA, Vahteristo P. Exome sequencing reveals three novel candidate predisposition genes for diffuse gastric cancer. *Fam Cancer* 2015; **14**: 241-246 [PMID: 25576241 DOI: 10.1007/s10689-015-9778-z]

30 **He LJ**, Cai MY, Xu GL, Li JJ, Weng ZJ, Xu DZ, Luo GY, Zhu SL, Xie D. Prognostic significance of overexpression of EZH2 and H3k27me3 proteins in gastric cancer. *Asian Pac J Cancer Prev* 2012; **13**: 3173-3178 [PMID: 22994729 DOI: 10.7314/apjcp.2012.13.7.3173]

31 **Nishikawaji T**, Akiyama Y, Shimada S, Kojima K, Kawano T, Eishi Y, Yuasa Y, Tanaka S. Oncogenic roles of the SETDB2 histone methyltransferase in gastric cancer. *Oncotarget* 2016; **7**: 67251-67265 [PMID: 27572307 DOI: 10.18632/oncotarget.11625]

32 **Elmaci İ**, Altinoz MA, Sari R, Bolukbasi FH. Phosphorylated Histone H3 (PHH3) as a Novel Cell Proliferation Marker and Prognosticator for Meningeal Tumors: A Short Review. *Appl Immunohistochem Mol Morphol* 2018; **26**: 627-631 [PMID: 28777144 DOI: 10.1097/PAI.0000000000000499]

33 **Besant PG**, Attwood PV. Histone H4 histidine phosphorylation: kinases, phosphatases, liver regeneration and cancer. *Biochem Soc Trans* 2012; **40**: 290-293 [PMID: 22260708 DOI: 10.1042/BST20110605]

34 **Ajiro K**, Yoda K, Utsumi K, Nishikawa Y. Alteration of cell cycle-dependent histone phosphorylations by okadaic acid. Induction of mitosis-specific H3 phosphorylation and chromatin condensation in mammalian interphase cells. *J Biol Chem* 1996; **271**: 13197-13201 [PMID: 8662672 DOI: 10.1074/jbc.271.22.13197]

35 **Humphrey SJ**, James DE, Mann M. Protein Phosphorylation: A Major Switch Mechanism for Metabolic Regulation. *Trends Endocrinol Metab* 2015; **26**: 676-687 [PMID: 26498855 DOI: 10.1016/j.tem.2015.09.013]

36 **Murakami Y**. Phosphorylation of repressive histone code readers by casein kinase 2 plays diverse roles in heterochromatin regulation. *J Biochem* 2019; **166**: 3-6 [PMID: 31198932 DOI: 10.1093/jb/mvz045]

37 **Qi H**, Yang Z, Dai C, Wang R, Ke X, Zhang S, Xiang X, Chen K, Li C, Luo J, Shao J, Shen J. STAT3 activates MSK1-mediated histone H3 phosphorylation to promote NFAT signaling in gastric carcinogenesis. *Oncogenesis* 2020; **9**: 15 [PMID: 32041943 DOI: 10.1038/s41389-020-0195-2]

38 **Khan SA**, Amnekar R, Khade B, Barreto SG, Ramadwar M, Shrikhande SV, Gupta S. p38-MAPK/MSK1-mediated overexpression of histone H3 serine 10 phosphorylation defines distance-dependent prognostic value of negative resection margin in gastric cancer. *Clin Epigenetics* 2016; **8**: 88 [PMID: 27588146 DOI: 10.1186/s13148-016-0255-9]

39 **Takahashi H**, Murai Y, Tsuneyama K, Nomoto K, Okada E, Fujita H, Takano Y. Overexpression of phosphorylated histone H3 is an indicator of poor prognosis in gastric adenocarcinoma patients. *Appl Immunohistochem Mol Morphol* 2006; **14**: 296-302 [PMID: 16932020 DOI: 10.1097/00129039-200609000-00007]

40 **Xu J**, Tian F, Chen X, Liu Z, Wu C, Zhao Z. Ras-ERK1/2 signaling participates in the progression of gastric cancer through repressing Aurora B-mediated H1.4 phosphorylation at Ser27. *J Cell Physiol* 2020 [PMID: 31907925 DOI: 10.1002/jcp.29432]

41 **Wang J**, Qiu Z, Wu Y. Ubiquitin Regulation: The Histone Modifying Enzyme's Story. *Cells* 2018; **7** [PMID: 30150556 DOI: 10.3390/cells7090118]

42 **Swatek KN**, Komander D. Ubiquitin modifications. *Cell Res* 2016; **26**: 399-422 [PMID: 27012465 DOI: 10.1038/cr.2016.39]

43 **Wilkinson KD**. Regulation of ubiquitin-dependent processes by deubiquitinating enzymes. *FASEB J* 1997; **11**: 1245-1256 [PMID: 9409543 DOI: 10.1096/fasebj.11.14.9409543]

44 **Eletr ZM**, Wilkinson KD. Regulation of proteolysis by human deubiquitinating enzymes. *Biochim Biophys Acta* 2014; **1843**: 114-128 [PMID: 23845989 DOI: 10.1016/j.bbamcr.2013.06.027]

45 **Hahn MA**, Dickson KA, Jackson S, Clarkson A, Gill AJ, Marsh DJ. The tumor suppressor CDC73 interacts with the ring finger proteins RNF20 and RNF40 and is required for the maintenance of histone 2B monoubiquitination. *Hum Mol Genet* 2012; **21**: 559-568 [PMID: 22021426 DOI: 10.1093/hmg/ddr490]

46 **Wang ZJ**, Yang JL, Wang YP, Lou JY, Chen J, Liu C, Guo LD. Decreased histone H2B monoubiquitination in malignant gastric carcinoma. *World J Gastroenterol* 2013; **19**: 8099-8107 [PMID: 24307806 DOI: 10.3748/wjg.v19.i44.8099]

47 **Zhang Q**, Wu Y, Xu Q, Ma F, Zhang CY. Recent advances in biosensors for in vitro detection and in vivo imaging of DNA methylation. *Biosens Bioelectron* 2021; **171**: 112712 [PMID: 33045657 DOI: 10.1016/j.bios.2020.112712]

48 **Ortiz-Barahona V**, Joshi RS, Esteller M. Use of DNA methylation profiling in translational oncology. *Semin Cancer Biol* 2020 [PMID: 33352265 DOI: 10.1016/j.semcancer.2020.12.011]

49 **Gardiner-Garden M**, Frommer M. CpG islands in vertebrate genomes. *J Mol Biol* 1987; **196**: 261-282 [PMID: 3656447 DOI: 10.1016/0022-2836(87)90689-9]

50 **Héberlé É**, Bardet AF. Sensitivity of transcription factors to DNA methylation. *Essays Biochem* 2019; **63**: 727-741 [PMID: 31755929 DOI: 10.1042/EBC20190033]

51 **Wang M**, Li Y, Gao J, Li Y, Zhou J, Gu L, Shen L, Deng D. p16 Methylation is associated with chemosensitivity to fluorouracil in patients with advanced gastric cancer. *Med Oncol* 2014; **31**: 988 [PMID: 24816738 DOI: 10.1007/s12032-014-0988-2]

52 **Balgkouranidou I**, Matthaios D, Karayiannakis A, Bolanaki H, Michailidis P, Xenidis N, Amarantidis K, Chelis L, Trypsianis G, Chatzaki E, Lianidou ES, Kakolyris S. Prognostic role of APC and RASSF1A promoter methylation status in cell free circulating DNA of operable gastric cancer patients. *Mutat Res* 2015; **778**: 46-51 [PMID: 26073472 DOI: 10.1016/j.mrfmmm.2015.05.002]

53 **Yang X**, Han H, De Carvalho DD, Lay FD, Jones PA, Liang G. Gene body methylation can alter gene expression and is a therapeutic target in cancer. *Cancer Cell* 2014; **26**: 577-590 [PMID: 25263941 DOI: 10.1016/j.ccr.2014.07.028]

54 **Kim Y**, Wen X, Jeong S, Cho NY, Kim WH, Kang GH. Combinatory low methylation statuses of SAT-α and L1 are associated with shortened survival time in patients with advanced gastric cancer. *Gastric Cancer* 2019; **22**: 37-47 [PMID: 29926315 DOI: 10.1007/s10120-018-0852-8]

55 **Kurklu B**, Whitehead RH, Ong EK, Minamoto T, Fox JG, Mann JR, Judd LM, Giraud AS, Menheniott TR. Lineage-specific RUNX3 hypomethylation marks the preneoplastic immune component of gastric cancer. *Oncogene* 2015; **34**: 2856-2866 [PMID: 25088199 DOI: 10.1038/onc.2014.233]

56 **Leodolter A**, Alonso S, González B, Ebert MP, Vieth M, Röcken C, Wex T, Peitz U, Malfertheiner P, Perucho M. Somatic DNA Hypomethylation in H. pylori-Associated High-Risk Gastritis and Gastric Cancer: Enhanced Somatic Hypomethylation Associates with Advanced Stage Cancer. *Clin Transl Gastroenterol* 2015; **6**: e85 [PMID: 25928808 DOI: 10.1038/ctg.2015.14]

57 **Leung WK**, Man EP, Yu J, Go MY, To KF, Yamaoka Y, Cheng VY, Ng EK, Sung JJ. Effects of Helicobacter pylori eradication on methylation status of E-cadherin gene in noncancerous stomach. *Clin Cancer Res* 2006; **12**: 3216-3221 [PMID: 16707623 DOI: 10.1158/1078-0432.Ccr-05-2442]

58 **Perri F**, Cotugno R, Piepoli A, Merla A, Quitadamo M, Gentile A, Pilotto A, Annese V, Andriulli A. Aberrant DNA methylation in non-neoplastic gastric mucosa of H. Pylori infected patients and effect of eradication. *Am J Gastroenterol* 2007; **102**: 1361-1371 [PMID: 17509026 DOI: 10.1111/j.1572-0241.2007.01284.x]

59 **Niwa T**, Toyoda T, Tsukamoto T, Mori A, Tatematsu M, Ushijima T. Prevention of Helicobacter pylori-induced gastric cancers in gerbils by a DNA demethylating agent. *Cancer Prev Res (Phila)* 2013; **6**: 263-270 [PMID: 23559452 DOI: 10.1158/1940-6207.Capr-12-0369]

60 **Nakajima T**, Enomoto S, Yamashita S, Ando T, Nakanishi Y, Nakazawa K, Oda I, Gotoda T, Ushijima T. Persistence of a component of DNA methylation in gastric mucosae after Helicobacter pylori eradication. *J Gastroenterol* 2010; **45**: 37-44 [PMID: 19821005 DOI: 10.1007/s00535-009-0142-7]

61 **Park JH**, Park J, Choi JK, Lyu J, Bae MG, Lee YG, Bae JB, Park DY, Yang HK, Kim TY, Kim YJ. Identification of DNA methylation changes associated with human gastric cancer. *BMC Med Genomics* 2011; **4**: 82 [PMID: 22133303 DOI: 10.1186/1755-8794-4-82]

62 **Muhammad JS**, Eladl MA, Khoder G. *Helicobacter pylori*-induced DNA Methylation as an Epigenetic Modulator of Gastric Cancer: Recent Outcomes and Future Direction. *Pathogens* 2019; **8** [PMID: 30781778 DOI: 10.3390/pathogens8010023]

63 **Tekcham DS**, Tiwari PK. Non-coding RNAs as emerging molecular targets of gallbladder cancer. *Gene* 2016; **588**: 79-85 [PMID: 27131889 DOI: 10.1016/j.gene.2016.04.047]

64 **Lee RC**, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993; **75**: 843-854 [PMID: 8252621 DOI: 10.1016/0092-8674(93)90529-y]

65 **Reinhart BJ**, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, Horvitz HR, Ruvkun G. The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. *Nature* 2000; **403**: 901-906 [PMID: 10706289 DOI: 10.1038/35002607]

66 **Tsai MM**, Wang CS, Tsai CY, Huang HW, Chi HC, Lin YH, Lu PH, Lin KH. Potential Diagnostic, Prognostic and Therapeutic Targets of MicroRNAs in Human Gastric Cancer. *Int J Mol Sci* 2016; **17** [PMID: 27322246 DOI: 10.3390/ijms17060945]

67 **Wang J**, Sun J, Wang J, Song Y, Gao P, Shi J, Chen P, Wang Z. Long noncoding RNAs in gastric cancer: functions and clinical applications. *Onco Targets Ther* 2016; **9**: 681-697 [PMID: 26929639 DOI: 10.2147/OTT.S95412]

68 **Bartel DP**. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; **136**: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]

69 **Ueda T**, Volinia S, Okumura H, Shimizu M, Taccioli C, Rossi S, Alder H, Liu CG, Oue N, Yasui W, Yoshida K, Sasaki H, Nomura S, Seto Y, Kaminishi M, Calin GA, Croce CM. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncol* 2010; **11**: 136-146 [PMID: 20022810 DOI: 10.1016/S1470-2045(09)70343-2]

70 **Yu L**, Wu D, Gao H, Balic JJ, Tsykin A, Han TS, Liu YD, Kennedy CL, Li JK, Mao JQ, Tan P, Oshima M, Goodall GJ, Jenkins BJ. Clinical Utility of a STAT3-Regulated miRNA-200 Family Signature with Prognostic Potential in Early Gastric Cancer. *Clin Cancer Res* 2018; **24**: 1459-1472 [PMID: 29330205 DOI: 10.1158/1078-0432.CCR-17-2485]

71 **Mercer TR**, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet* 2009; **10**: 155-159 [PMID: 19188922 DOI: 10.1038/nrg2521]

72 **Marchese FP**, Huarte M. Long non-coding RNAs and chromatin modifiers: their place in the epigenetic code. *Epigenetics* 2014; **9**: 21-26 [PMID: 24335342 DOI: 10.4161/epi.27472]

73 **Prasanth KV**, Prasanth SG, Xuan Z, Hearn S, Freier SM, Bennett CF, Zhang MQ, Spector DL. Regulating gene expression through RNA nuclear retention. *Cell* 2005; **123**: 249-263 [PMID: 16239143 DOI: 10.1016/j.cell.2005.08.033]

74 **Clemson CM**, Hutchinson JN, Sara SA, Ensminger AW, Fox AH, Chess A, Lawrence JB. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. *Mol Cell* 2009; **33**: 717-726 [PMID: 19217333 DOI: 10.1016/j.molcel.2009.01.026]

75 **Bie L**, Luo S, Li D, Wei Y, Mu Y, Chen X, Wang S, Guo P, Lu X. HOTAIR Competitively Binds MiRNA330 as a Molecular Sponge to Increase the Resistance of Gastric Cancer to Trastuzumab. *Curr Cancer Drug Targets* 2020; **20**: 700-709 [PMID: 32364078 DOI: 10.2174/1568009620666200504114000]

76 **Endo H**, Shiroki T, Nakagawa T, Yokoyama M, Tamai K, Yamanami H, Fujiya T, Sato I, Yamaguchi K, Tanaka N, Iijima K, Shimosegawa T, Sugamura K, Satoh K. Enhanced expression of long non-coding RNA HOTAIR is associated with the development of gastric cancer. *PLoS One* 2013; **8**: e77070 [PMID: 24130837 DOI: 10.1371/journal.pone.0077070]

77 **Cheng C**, Qin Y, Zhi Q, Wang J, Qin C. Knockdown of long non-coding RNA HOTAIR inhibits cisplatin resistance of gastric cancer cells through inhibiting the PI3K/Akt and Wnt/β-catenin signaling pathways by up-regulating miR-34a. *Int J Biol Macromol* 2018; **107**: 2620-2629 [PMID: 29080815 DOI: 10.1016/j.ijbiomac.2017.10.154]

78 **Xue M**, Chen LY, Wang WJ, Su TT, Shi LH, Wang L, Zhang W, Si JM, Wang LJ, Chen SJ. HOTAIR induces the ubiquitination of Runx3 by interacting with Mex3b and enhances the invasion of gastric cancer cells. *Gastric Cancer* 2018; **21**: 756-764 [PMID: 29417297 DOI: 10.1007/s10120-018-0801-6]

79 **Tang X**, Ren H, Guo M, Qian J, Yang Y, Gu C. Review on circular RNAs and new insights into their roles in cancer. *Comput Struct Biotechnol J* 2021; **19**: 910-928 [PMID: 33598105 DOI: 10.1016/j.csbj.2021.01.018]

80 **Ruan Y**, Li Z, Shen Y, Li T, Zhang H, Guo J. Functions of circular RNAs and their potential applications in gastric cancer. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 85-92 [PMID: 31922886 DOI: 10.1080/17474124.2020.1715211]

81 **Zhang M**, Huang N, Yang X, Luo J, Yan S, Xiao F, Chen W, Gao X, Zhao K, Zhou H, Li Z, Ming L, Xie B, Zhang N. A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis. *Oncogene* 2018; **37**: 1805-1814 [PMID: 29343848 DOI: 10.1038/s41388-017-0019-9]

82 **Pamudurti NR**, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, Hanan M, Wyler E, Perez-Hernandez D, Ramberger E, Shenzis S, Samson M, Dittmar G, Landthaler M, Chekulaeva M, Rajewsky N, Kadener S. Translation of CircRNAs. *Mol Cell* 2017; **66**: 9-21.e7 [PMID: 28344080 DOI: 10.1016/j.molcel.2017.02.021]

83 **Guarnerio J**, Bezzi M, Jeong JC, Paffenholz SV, Berry K, Naldini MM, Lo-Coco F, Tay Y, Beck AH, Pandolfi PP. Oncogenic Role of Fusion-circRNAs Derived from Cancer-Associated Chromosomal Translocations. *Cell* 2016; **166**: 1055-1056 [PMID: 27518567 DOI: 10.1016/j.cell.2016.07.035]

84 **Pan H**, Li T, Jiang Y, Pan C, Ding Y, Huang Z, Yu H, Kong D. Overexpression of Circular RNA ciRS-7 Abrogates the Tumor Suppressive Effect of miR-7 on Gastric Cancer via PTEN/PI3K/AKT Signaling Pathway. *J Cell Biochem* 2018; **119**: 440-446 [PMID: 28608528 DOI: 10.1002/jcb.26201]

85 **Tsujiura M**, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Otsuji E. Liquid biopsy of gastric cancer patients: circulating tumor cells and cell-free nucleic acids. *World J Gastroenterol* 2014; **20**: 3265-3286 [PMID: 24696609 DOI: 10.3748/wjg.v20.i12.3265]

86 **Li W**, Zhang X, Lu X, You L, Song Y, Luo Z, Zhang J, Nie J, Zheng W, Xu D, Wang Y, Dong Y, Yu S, Hong J, Shi J, Hao H, Luo F, Hua L, Wang P, Qian X, Yuan F, Wei L, Cui M, Zhang T, Liao Q, Dai M, Liu Z, Chen G, Meckel K, Adhikari S, Jia G, Bissonnette MB, Zhang X, Zhao Y, Zhang W, He C, Liu J. 5-Hydroxymethylcytosine signatures in circulating cell-free DNA as diagnostic biomarkers for human cancers. *Cell Res* 2017; **27**: 1243-1257 [PMID: 28925386 DOI: 10.1038/cr.2017.121]

87 **Amini M**, Ghorban K, Mokhtarzadeh A, Dadmanesh M, Baradaran B. CD40 DNA hypermethylation in primary gastric tumors; as a novel diagnostic biomarker. *Life Sci* 2020; **254**: 117774 [PMID: 32407843 DOI: 10.1016/j.lfs.2020.117774]

88 **Amini M**, Foroughi K, Talebi F, Aghagolzade Haji H, Kamali F, Jandaghi P, Hoheisel JD, Manoochehri M. GHSR DNA hypermethylation is a new epigenetic biomarker for gastric adenocarcinoma and beyond. *J Cell Physiol* 2019 [PMID: 30677130 DOI: 10.1002/jcp.28179]

89 **Xu G**, Meng L, Yuan D, Li K, Zhang Y, Dang C, Zhu K. MEG3/miR‑21 axis affects cell mobility by suppressing epithelial‑mesenchymal transition in gastric cancer. *Oncol Rep* 2018; **40**: 39-48 [PMID: 29749532 DOI: 10.3892/or.2018.6424]

90 **Yuan Y**, Zhang Y, Han L, Sun S, Shu Y. miR-183 inhibits autophagy and apoptosis in gastric cancer cells by targeting ultraviolet radiation resistance-associated gene. *Int J Mol Med* 2018; **42**: 3562-3570 [PMID: 30221685 DOI: 10.3892/ijmm.2018.3871]

91 **Lin W**, Miao Y, Meng X, Huang Y, Zhao W, Ruan J. miRNA-765 mediates multidrug resistance via targeting BATF2 in gastric cancer cells. *FEBS Open Bio* 2020; **10**: 1021-1030 [PMID: 32166887 DOI: 10.1002/2211-5463.12838]

92 **Shi SS**, Zhang HP, Yang CQ, Li LN, Shen Y, Zhang YQ. Exosomal miR-155-5p promotes proliferation and migration of gastric cancer cells by inhibiting TP53INP1 expression. *Pathol Res Pract* 2020; **216**: 152986 [PMID: 32527448 DOI: 10.1016/j.prp.2020.152986]

93 **Ding L**, Li Q, Chakrabarti J, Munoz A, Faure-Kumar E, Ocadiz-Ruiz R, Razumilava N, Zhang G, Hayes MH, Sontz RA, Mendoza ZE, Mahurkar S, Greenson JK, Perez-Perez G, Hanh NTH, Zavros Y, Samuelson LC, Iliopoulos D, Merchant JL. MiR130b from Schlafen4+ MDSCs stimulates epithelial proliferation and correlates with preneoplastic changes prior to gastric cancer. *Gut* 2020; **69**: 1750-1761 [PMID: 31980446 DOI: 10.1136/gutjnl-2019-318817]

94 **Li T**, Guo H, Li H, Jiang Y, Zhuang K, Lei C, Wu J, Zhou H, Zhu R, Zhao X, Lu Y, Shi C, Nie Y, Wu K, Yuan Z, Fan DM, Shi Y. MicroRNA-92a-1-5p increases CDX2 by targeting FOXD1 in bile acids-induced gastric intestinal metaplasia. *Gut* 2019; **68**: 1751-1763 [PMID: 30635407 DOI: 10.1136/gutjnl-2017-315318]

95 **Han TS**, Voon DC, Oshima H, Nakayama M, Echizen K, Sakai E, Yong ZWE, Murakami K, Yu L, Minamoto T, Ock CY, Jenkins BJ, Kim SJ, Yang HK, Oshima M. Interleukin 1 Up-regulates MicroRNA 135b to Promote Inflammation-Associated Gastric Carcinogenesis in Mice. *Gastroenterology* 2019; **156**: 1140-1155.e4 [PMID: 30508510 DOI: 10.1053/j.gastro.2018.11.059]

96 **Lu Z**, Luo T, Pang T, Du Z, Yin X, Cui H, Fang G, Xue X. MALAT1 promotes gastric adenocarcinoma through the MALAT1/miR-181a-5p/AKT3 axis. *Open Biol* 2019; **9**: 190095 [PMID: 31480991 DOI: 10.1098/rsob.190095]

97 **Xia M**, Wei J, Tong K. MiR-224 promotes proliferation and migration of gastric cancer cells through targeting PAK4. *Pharmazie* 2016; **71**: 460-464 [PMID: 29442033 DOI: 10.1691/ph.2016.6580]

98 **Shi Y**, Duan Z, Zhang X, Zhang X, Wang G, Li F. Down-regulation of the let-7i facilitates gastric cancer invasion and metastasis by targeting COL1A1. *Protein Cell* 2019; **10**: 143-148 [PMID: 29858755 DOI: 10.1007/s13238-018-0550-7]

99 **Shomali N**, Shirafkan N, Duijf PHG, Ghasabi M, Babaloo Z, Yousefi M, Mansoori B, Asadi M, Shanehbandi D, Baghbani E, Mohammadi A, Baradaran B. Downregulation of miR-146a promotes cell migration in Helicobacter pylori-negative gastric cancer. *J Cell Biochem* 2019; **120**: 9495-9505 [PMID: 30537266 DOI: 10.1002/jcb.28225]

100 **Zhang W**, Liao K, Liu D. MiRNA-12129 Suppresses Cell Proliferation and Block Cell Cycle Progression by Targeting SIRT1 in GASTRIC Cancer. *Technol Cancer Res Treat* 2020; **19**: 1533033820928144 [PMID: 32508267 DOI: 10.1177/1533033820928144]

101 **Feng Q**, Wu X, Li F, Ning B, Lu X, Zhang Y, Pan Y, Guan W. miR-27b inhibits gastric cancer metastasis by targeting NR2F2. *Protein Cell* 2017; **8**: 114-122 [PMID: 27844448 DOI: 10.1007/s13238-016-0340-z]

102 **Wu K**, Zou J, Lin C, Jie ZG. MicroRNA-140-5p inhibits cell proliferation, migration and promotes cell apoptosis in gastric cancer through the negative regulation of THY1-mediated Notch signaling. *Biosci Rep* 2019; **39** [PMID: 31123165 DOI: 10.1042/bsr20181434]

103 **Zhang Y**, Yuan Y, Zhang Y, Cheng L, Zhou X, Chen K. SNHG7 accelerates cell migration and invasion through regulating miR-34a-Snail-EMT axis in gastric cancer. *Cell Cycle* 2020; **19**: 142-152 [PMID: 31814518 DOI: 10.1080/15384101.2019.1699753]

104 **Fan Y**, Shi Y, Lin Z, Huang X, Li J, Huang W, Shen D, Zhuang G, Liu W. miR-9-5p Suppresses Malignant Biological Behaviors of Human Gastric Cancer Cells by Negative Regulation of TNFAIP8L3. *Dig Dis Sci* 2019; **64**: 2823-2829 [PMID: 31140050 DOI: 10.1007/s10620-019-05626-2]

105 **Wang CQ**. MiR-195 reverses 5-FU resistance through targeting HMGA1 in gastric cancer cells. *Eur Rev Med Pharmacol Sci* 2019; **23**: 3771-3778 [PMID: 31115003 DOI: 10.26355/eurrev\_201905\_17803]

106 **Li Y**, Wang K, Wei Y, Yao Q, Zhang Q, Qu H, Zhu G. lncRNA-MIAT regulates cell biological behaviors in gastric cancer through a mechanism involving the miR-29a-3p/HDAC4 axis. *Oncol Rep* 2017; **38**: 3465-3472 [PMID: 29039602 DOI: 10.3892/or.2017.6020]

107 **Liu J**, Ben Q, Lu E, He X, Yang X, Ma J, Zhang W, Wang Z, Liu T, Zhang J, Wang H. Long noncoding RNA PANDAR blocks CDKN1A gene transcription by competitive interaction with p53 protein in gastric cancer. *Cell Death Dis* 2018; **9**: 168 [PMID: 29416011 DOI: 10.1038/s41419-017-0246-6]

108 **Xu TP**, Wang WY, Ma P, Shuai Y, Zhao K, Wang YF, Li W, Xia R, Chen WM, Zhang EB, Shu YQ. Upregulation of the long noncoding RNA FOXD2-AS1 promotes carcinogenesis by epigenetically silencing EphB3 through EZH2 and LSD1, and predicts poor prognosis in gastric cancer. *Oncogene* 2018; **37**: 5020-5036 [PMID: 29789713 DOI: 10.1038/s41388-018-0308-y]

109 **Yuan H**, Chen Z, Bai S, Wei H, Wang Y, Ji R, Guo Q, Li Q, Ye Y, Wu J, Zhou Y, Qiao L. Molecular mechanisms of lncRNA SMARCC2/miR-551b-3p/TMPRSS4 axis in gastric cancer. *Cancer Lett* 2018; **418**: 84-96 [PMID: 29337109 DOI: 10.1016/j.canlet.2018.01.032]

110 **Sun L**, Li J, Yan W, Yao Z, Wang R, Zhou X, Wu H, Zhang G, Shi T, Chen W. H19 promotes aerobic glycolysis, proliferation, and immune escape of gastric cancer cells through the microRNA-519d-3p/lactate dehydrogenase A axis. *Cancer Sci* 2021; **112**: 2245-2259 [PMID: 33756038 DOI: 10.1111/cas.14896]

111 **Xu TP**, Wang YF, Xiong WL, Ma P, Wang WY, Chen WM, Huang MD, Xia R, Wang R, Zhang EB, Liu YW, De W, Shu YQ. E2F1 induces TINCR transcriptional activity and accelerates gastric cancer progression via activation of TINCR/STAU1/CDKN2B signaling axis. *Cell Death Dis* 2017; **8**: e2837 [PMID: 28569791 DOI: 10.1038/cddis.2017.205]

112 **Wang YJ**, Liu JZ, Lv P, Dang Y, Gao JY, Wang Y. Long non-coding RNA CCAT2 promotes gastric cancer proliferation and invasion by regulating the E-cadherin and LATS2. *Am J Cancer Res* 2016; **6**: 2651-2660 [PMID: 27904778]

113 **Zhang K**, Lu C, Huang X, Cui J, Li J, Gao Y, Liang W, Liu Y, Sun Y, Liu H, Wei B, Chen L. Long noncoding RNA *AOC4P* regulates tumor cell proliferation and invasion by epithelial-mesenchymal transition in gastric cancer. *Therap Adv Gastroenterol* 2019; **12**: 1756284819827697 [PMID: 30815034 DOI: 10.1177/1756284819827697]

114 **Zong W**, Feng W, Jiang Y, Ju S, Cui M, Jing R. Evaluating the diagnostic and prognostic value of serum long non-coding RNA CTC-497E21.4 in gastric cancer. *Clin Chem Lab Med* 2019; **57**: 1063-1072 [PMID: 30763257 DOI: 10.1515/cclm-2018-0929]

115 **Miao X**, Liu Y, Fan Y, Wang G, Zhu H. LncRNA BANCR Attenuates the Killing Capacity of Cisplatin on Gastric Cancer Cell Through the ERK1/2 Pathway. *Cancer Manag Res* 2021; **13**: 287-296 [PMID: 33469371 DOI: 10.2147/CMAR.S269679]

116 **Zhang ZX**, Liu ZQ, Jiang B, Lu XY, Ning XF, Yuan CT, Wang AL. BRAF activated non-coding RNA (BANCR) promoting gastric cancer cells proliferation via regulation of NF-κB1. *Biochem Biophys Res Commun* 2015; **465**: 225-231 [PMID: 26248136 DOI: 10.1016/j.bbrc.2015.07.158]

117 **Xiao ZS**, Long H, Zhao L, Li HX, Zhang XN. LncRNA HOTTIP promotes proliferation and inhibits apoptosis of gastric carcinoma cells via adsorbing miR-615-3p. *Eur Rev Med Pharmacol Sci* 2020; **24**: 6692-6698 [PMID: 32633359 DOI: 10.26355/eurrev\_202006\_21656]

118 **Zhao R**, Zhang X, Zhang Y, Zhang Y, Yang Y, Sun Y, Zheng X, Qu A, Umwali Y, Zhang Y. HOTTIP Predicts Poor Survival in Gastric Cancer Patients and Contributes to Cisplatin Resistance by Sponging miR-216a-5p. *Front Cell Dev Biol* 2020; **8**: 348 [PMID: 32457911 DOI: 10.3389/fcell.2020.00348]

119 **Liu J**, Wang J, Song Y, Ma B, Luo J, Ni Z, Gao P, Sun J, Zhao J, Chen X, Wang Z. A panel consisting of three novel circulating lncRNAs, is it a predictive tool for gastric cancer? *J Cell Mol Med* 2018; **22**: 3605-3613 [PMID: 29700972 DOI: 10.1111/jcmm.13640]

120 **Ke D**, Li H, Zhang Y, An Y, Fu H, Fang X, Zheng X. The combination of circulating long noncoding RNAs AK001058, INHBA-AS1, MIR4435-2HG, and CEBPA-AS1 fragments in plasma serve as diagnostic markers for gastric cancer. *Oncotarget* 2017; **8**: 21516-21525 [PMID: 28423525 DOI: 10.18632/oncotarget.15628]

121 **Wei F**, Wang Y, Zhou Y, Li Y. Long noncoding RNA CYTOR triggers gastric cancer progression by targeting miR-103/RAB10. *Acta Biochim Biophys Sin (Shanghai)* 2021; **53**: 1044-1054 [PMID: 34110382 DOI: 10.1093/abbs/gmab071]

122 **Teng F**, Zhang JX, Chen Y, Shen XD, Su C, Guo YJ, Wang PH, Shi CC, Lei M, Cao YO, Liu SQ. LncRNA NKX2-1-AS1 promotes tumor progression and angiogenesis via upregulation of SERPINE1 expression and activation of the VEGFR-2 signaling pathway in gastric cancer. *Mol Oncol* 2021; **15**: 1234-1255 [PMID: 33512745 DOI: 10.1002/1878-0261.12911]

123 **Xu Y**, Li Y, Qiu Y, Sun F, Zhu G, Sun J, Cai G, Lin W, Fu Y, Wu H, Jiang S, Wen Z, Feng F, Luo J, Yang Y, Zhang Q. LncRNA NEAT1 Promotes Gastric Cancer Progression Through miR-17-5p/TGFβR2 Axis Up-Regulated Angiogenesis. *Front Cell Dev Biol* 2021; **9**: 705697 [PMID: 34552925 DOI: 10.3389/fcell.2021.705697]

124 **Zhu T**, Wang Z, Wang G, Hu Z, Ding H, Li R, Sun J. Long non-coding RNA ZFAS1 promotes the expression of EPAS1 in gastric cardia adenocarcinoma. *J Adv Res* 2021; **28**: 7-15 [PMID: 33364040 DOI: 10.1016/j.jare.2020.06.006]

125 **Ma ZH**, Shuai Y, Gao XY, Yan Y, Wang KM, Wen XZ, Ji JF. BTEB2-Activated lncRNA TSPEAR-AS2 Drives GC Progression through Suppressing GJA1 Expression and Upregulating CLDN4 Expression. *Mol Ther Nucleic Acids* 2020; **22**: 1129-1141 [PMID: 33294297 DOI: 10.1016/j.omtn.2020.10.022]

126 **Song S**, He X, Wang J, Song H, Wang Y, Liu Y, Zhou Z, Yu Z, Miao D, Xue Y. A novel long noncoding RNA, TMEM92-AS1, promotes gastric cancer progression by binding to YBX1 to mediate CCL5. *Mol Oncol* 2021; **15**: 1256-1273 [PMID: 33247987 DOI: 10.1002/1878-0261.12863]

127 **Xin L**, Zhou LQ, Liu C, Zeng F, Yuan YW, Zhou Q, Li SH, Wu Y, Wang JL, Wu DZ, Lu H. Transfer of LncRNA CRNDE in TAM-derived exosomes is linked with cisplatin resistance in gastric cancer. *EMBO Rep* 2021; **22**: e52124 [PMID: 34647680 DOI: 10.15252/embr.202052124]

128 **Ding L**, Tian Y, Wang L, Bi M, Teng D, Hong S. Hypermethylated long noncoding RNA MEG3 promotes the progression of gastric cancer. *Aging (Albany NY)* 2019; **11**: 8139-8155 [PMID: 31584879 DOI: 10.18632/aging.102309]

129 **Cai C**, Zhang H, Zhu Y, Zheng P, Xu Y, Sun J, Zhang M, Lan T, Gu B, Li S, Ma P. Serum Exosomal Long Noncoding RNA pcsk2-2:1 As A Potential Novel Diagnostic Biomarker For Gastric Cancer. *Onco Targets Ther* 2019; **12**: 10035-10041 [PMID: 31819499 DOI: 10.2147/OTT.S229033]

130 **Li S**, Zhang M, Zhang H, Hu K, Cai C, Wang J, Shi L, Ma P, Xu Y, Zheng P. Exosomal long noncoding RNA lnc-GNAQ-6:1 may serve as a diagnostic marker for gastric cancer. *Clin Chim Acta* 2020; **501**: 252-257 [PMID: 31730812 DOI: 10.1016/j.cca.2019.10.047]

131 **Pan T**, Yu Z, Jin Z, Wu X, Wu A, Hou J, Chang X, Fan Z, Li J, Yu B, Li F, Yan C, Yang Z, Zhu Z, Liu B, Su L. Tumor suppressor lnc-CTSLP4 inhibits EMT and metastasis of gastric cancer by attenuating HNRNPAB-dependent Snail transcription. *Mol Ther Nucleic Acids* 2021; **23**: 1288-1303 [PMID: 33717650 DOI: 10.1016/j.omtn.2021.02.003]

132 **Xia Y**, Lv J, Jiang T, Li B, Li Y, He Z, Xuan Z, Sun G, Wang S, Li Z, Wang W, Wang L, Xu Z. CircFAM73A promotes the cancer stem cell-like properties of gastric cancer through the miR-490-3p/HMGA2 positive feedback loop and HNRNPK-mediated β-catenin stabilization. *J Exp Clin Cancer Res* 2021; **40**: 103 [PMID: 33731207 DOI: 10.1186/s13046-021-01896-9]

133 **Bu X**, Chen Z, Zhang A, Zhou X, Zhang X, Yuan H, Zhang Y, Yin C, Yan Y. Circular RNA circAFF2 accelerates gastric cancer development by activating miR-6894-5p and regulating ANTXR 1 expression. *Clin Res Hepatol Gastroenterol* 2021; **45**: 101671 [PMID: 33722777 DOI: 10.1016/j.clinre.2021.101671]

134 **Yang D**, Hu Z, Zhang Y, Zhang X, Xu J, Fu H, Zhu Z, Feng D, Cai Q. CircHIPK3 Promotes the Tumorigenesis and Development of Gastric Cancer Through miR-637/AKT1 Pathway. *Front Oncol* 2021; **11**: 637761 [PMID: 33680975 DOI: 10.3389/fonc.2021.637761]

135 **Deng P**, Sun M, Zhao WY, Hou B, Li K, Zhang T, Gu F. Circular RNA circVAPA promotes chemotherapy drug resistance in gastric cancer progression by regulating miR-125b-5p/STAT3 axis. *World J Gastroenterol* 2021; **27**: 487-500 [PMID: 33642823 DOI: 10.3748/wjg.v27.i6.487]

136 **Yang H**, Wu Z, Liu X, Chen M, Zhang X, Jiang Y. NFIB promotes the progression of gastric cancer by upregulating circMAP7D1 to stabilize HER2 mRNA. *Mol Med Rep* 2021; **23** [PMID: 33576439 DOI: 10.3892/mmr.2021.11908]

137 **Hua Y**, Wang H, Wang H, Wu X, Yang L, Wang C, Li X, Jin Y, Li M, Wang L, Dong C, Yin F. Circular RNA Circ\_0006282 Promotes Cell Proliferation and Metastasis in Gastric Cancer by Regulating MicroRNA-144-5p/Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein β Axis. *Cancer Manag Res* 2021; **13**: 815-827 [PMID: 33536789 DOI: 10.2147/CMAR.S283952]

138 **Xu Q**, Liao B, Hu S, Zhou Y, Xia W. Circular RNA 0081146 facilitates the progression of gastric cancer by sponging miR-144 and up-regulating HMGB1. *Biotechnol Lett* 2021; **43**: 767-779 [PMID: 33496921 DOI: 10.1007/s10529-020-03058-x]

139 **Wang L**, Li B, Yi X, Xiao X, Zheng Q, Ma L. Circ\_SMAD4 promotes gastric carcinogenesis by activating wnt/β-catenin pathway. *Cell Prolif* 2021; **54**: e12981 [PMID: 33458917 DOI: 10.1111/cpr.12981]

140 **Yu L**, Xie J, Liu X, Yu Y, Wang S. Plasma Exosomal CircNEK9 Accelerates the Progression of Gastric Cancer via miR-409-3p/MAP7 Axis. *Dig Dis Sci* 2021; **66**: 4274-4289 [PMID: 33449227 DOI: 10.1007/s10620-020-06816-z]

141 **Yue F**, Peng K, Zhang L, Zhang J. Circ\_0004104 Accelerates the Progression of Gastric Cancer by Regulating the miR-539-3p/RNF2 Axis. *Dig Dis Sci* 2021; **66**: 4290-4301 [PMID: 33449226 DOI: 10.1007/s10620-020-06802-5]

142 **Wang X**, Zhang Y, Li W, Liu X. Knockdown of cir\_RNA PVT1 Elevates Gastric Cancer Cisplatin Sensitivity via Sponging miR-152-3p. *J Surg Res* 2021; **261**: 185-195 [PMID: 33444948 DOI: 10.1016/j.jss.2020.12.013]

143 **Li J**, Yang Y, Xu D, Cao L. hsa\_circ\_0023409 Accelerates Gastric Cancer Cell Growth and Metastasis Through Regulating the IRS4/PI3K/AKT Pathway. *Cell Transplant* 2021; **30**: 963689720975390 [PMID: 33439739 DOI: 10.1177/0963689720975390]

144 **Yang Y**, Cai B, Shi X, Duan C, Tong T, Yu C. circ\_0044516 functions in the progression of gastric cancer by modulating MicroRNA-149-5p/HuR axis. *Mol Cell Biochem* 2021 [PMID: 33417162 DOI: 10.1007/s11010-020-04026-9]

145 **Cao J**, Zhang X, Xu P, Wang H, Wang S, Zhang L, Li Z, Xie L, Sun G, Xia Y, Lv J, Yang J, Xu Z. Circular RNA circLMO7 acts as a microRNA-30a-3p sponge to promote gastric cancer progression via the WNT2/β-catenin pathway. *J Exp Clin Cancer Res* 2021; **40**: 6 [PMID: 33397440 DOI: 10.1186/s13046-020-01791-9]

146 **Niu Q**, Dong Z, Liang M, Luo Y, Lin H, Lin M, Zhong X, Yao W, Weng J, Zhou X. Circular RNA hsa\_circ\_0001829 promotes gastric cancer progression through miR-155-5p/SMAD2 axis. *J Exp Clin Cancer Res* 2020; **39**: 280 [PMID: 33308284 DOI: 10.1186/s13046-020-01790-w]

147 **Pu Z**, Xu M, Yuan X, Xie H, Zhao J. Circular RNA circCUL3 Accelerates the Warburg Effect Progression of Gastric Cancer through Regulating the STAT3/HK2 Axis. *Mol Ther Nucleic Acids* 2020; **22**: 310-318 [PMID: 33230436 DOI: 10.1016/j.omtn.2020.08.023]

148 **Wang H**, Sun G, Xu P, Lv J, Zhang X, Zhang L, Wang S, Cao J, Xia Y, Xuan Z, Li B, Huang X, Jiang T, Fang L, Xu Z. Circular RNA TMEM87A promotes cell proliferation and metastasis of gastric cancer by elevating ULK1 via sponging miR-142-5p. *J Gastroenterol* 2021; **56**: 125-138 [PMID: 33155080 DOI: 10.1007/s00535-020-01744-1]

149 **Ma S**, Kong S, Gu X, Xu Y, Tao M, Shen L, Shen X, Ju S. As a biomarker for gastric cancer, circPTPN22 regulates the progression of gastric cancer through the EMT pathway. *Cancer Cell Int* 2021; **21**: 44 [PMID: 33430866 DOI: 10.1186/s12935-020-01701-1]

150 **Ma C**, Wang X, Yang F, Zang Y, Liu J, Wang X, Xu X, Li W, Jia J, Liu Z. Circular RNA hsa\_circ\_0004872 inhibits gastric cancer progression via the miR-224/Smad4/ADAR1 successive regulatory circuit. *Mol Cancer* 2020; **19**: 157 [PMID: 33172486 DOI: 10.1186/s12943-020-01268-5]

151 **Wang H**, Wang N, Zheng X, Wu L, Fan C, Li X, Ye K, Han S. Circular RNA hsa\_circ\_0009172 suppresses gastric cancer by regulation of microRNA-485-3p-mediated NTRK3. *Cancer Gene Ther* 2021; **28**: 1312-1324 [PMID: 33531648 DOI: 10.1038/s41417-020-00280-7]

152 **Li T**, Zuo X, Meng X. Circ\_002059 suppresses cell proliferation and migration of gastric cancer via miR-182/MTSS1 axis. *Acta Biochim Biophys Sin (Shanghai)* 2021; **53**: 454-462 [PMID: 33686422 DOI: 10.1093/abbs/gmab015]

153 **Wang Y**, Wang H, Zheng R, Wu P, Sun Z, Chen J, Zhang L, Zhang C, Qian H, Jiang J, Xu W. Circular RNA ITCH suppresses metastasis of gastric cancer via regulating miR-199a-5p/Klotho axis. *Cell Cycle* 2021; **20**: 522-536 [PMID: 33499704 DOI: 10.1080/15384101.2021.1878327]

154 **Peng L**, Sang H, Wei S, Li Y, Jin D, Zhu X, Li X, Dang Y, Zhang G. circCUL2 regulates gastric cancer malignant transformation and cisplatin resistance by modulating autophagy activation via miR-142-3p/ROCK2. *Mol Cancer* 2020; **19**: 156 [PMID: 33153478 DOI: 10.1186/s12943-020-01270-x]

155 **Sakakura C**, Hamada T, Miyagawa K, Nishio M, Miyashita A, Nagata H, Ida H, Yazumi S, Otsuji E, Chiba T, Ito K, Ito Y. Quantitative analysis of tumor-derived methylated RUNX3 sequences in the serum of gastric cancer patients. *Anticancer Res* 2009; **29**: 2619-2625 [PMID: 19596937]

156 **Kolesnikova EV**, Tamkovich SN, Bryzgunova OE, Shelestyuk PI, Permyakova VI, Vlassov VV, Tuzikov AS, Laktionov PP, Rykova EY. Circulating DNA in the blood of gastric cancer patients. *Ann N Y Acad Sci* 2008; **1137**: 226-231 [PMID: 18837952 DOI: 10.1196/annals.1448.009]

157 **Pimson C**, Ekalaksananan T, Pientong C, Promthet S, Putthanachote N, Suwanrungruang K, Wiangnon S. Aberrant methylation of PCDH10 and RASSF1A genes in blood samples for non-invasive diagnosis and prognostic assessment of gastric cancer. *PeerJ* 2016; **4**: e2112 [PMID: 27330867 DOI: 10.7717/peerj.2112]

158 **Kanda M**, Shimizu D, Fujii T, Sueoka S, Tanaka Y, Ezaka K, Takami H, Tanaka H, Hashimoto R, Iwata N, Kobayashi D, Tanaka C, Yamada S, Nakayama G, Sugimoto H, Koike M, Fujiwara M, Kodera Y. Function and diagnostic value of Anosmin-1 in gastric cancer progression. *Int J Cancer* 2016; **138**: 721-730 [PMID: 26270236 DOI: 10.1002/ijc.29803]

159 **Alarcón MA**, Olivares W, Córdova-Delgado M, Muñoz-Medel M, de Mayo T, Carrasco-Aviño G, Wichmann I, Landeros N, Amigo J, Norero E, Villarroel-Espíndola F, Riquelme A, Garrido M, Owen GI, Corvalán AH. The Reprimo-Like Gene Is an Epigenetic-Mediated Tumor Suppressor and a Candidate Biomarker for the Non-Invasive Detection of Gastric Cancer. *Int J Mol Sci* 2020; **21** [PMID: 33322837 DOI: 10.3390/ijms21249472]

160 **Nanishi K**, Konishi H, Shoda K, Arita T, Kosuga T, Komatsu S, Shiozaki A, Kubota T, Fujiwara H, Okamoto K, Ichikawa D, Otsuji E. Circulating circERBB2 as a potential prognostic biomarker for gastric cancer: An investigative study. *Cancer Sci* 2020; **111**: 4177-4186 [PMID: 32896032 DOI: 10.1111/cas.14645]

161 **Guo X**, Lv X, Ru Y, Zhou F, Wang N, Xi H, Zhang K, Li J, Chang R, Xie T, Wang X, Li B, Chen Y, Yang Y, Chen L, Chen L. Circulating Exosomal Gastric Cancer-Associated Long Noncoding RNA1 as a Biomarker for Early Detection and Monitoring Progression of Gastric Cancer: A Multiphase Study. *JAMA Surg* 2020; **155**: 572-579 [PMID: 32520332 DOI: 10.1001/jamasurg.2020.1133]

162 **Shin SJ**, Park S, Kim MH, Nam CM, Kim H, Choi YY, Jung MK, Choi HJ, Rha SY, Chung HC. Mesothelin Expression Is a Predictive Factor for Peritoneal Recurrence in Curatively Resected Stage III Gastric Cancer. *Oncologist* 2019; **24**: e1108-e1114 [PMID: 31015316 DOI: 10.1634/theoncologist.2018-0896]

163 **Liu X**, Chu KM. Exosomal miRNAs as circulating biomarkers for prediction of development of haematogenous metastasis after surgery for stage II/III gastric cancer. *J Cell Mol Med* 2020; **24**: 6220-6232 [PMID: 32383554 DOI: 10.1111/jcmm.15253]

164 **Zhao Z**, Zhang C, Zhao Q. S100A9 as a novel diagnostic and prognostic biomarker in human gastric cancer. *Scand J Gastroenterol* 2020; **55**: 338-346 [PMID: 32172630 DOI: 10.1080/00365521.2020.1737883]

165 **Hu J**, Yu J, Gan J, Song N, Shi L, Liu J, Zhang Z, Du J. Notch1/2/3/4 are prognostic biomarker and correlated with immune infiltrates in gastric cancer. *Aging (Albany NY)* 2020; **12**: 2595-2609 [PMID: 32028262 DOI: 10.18632/aging.102764]

166 **Meng X**, Zhao Y, Liu J, Wang L, Dong Z, Zhang T, Gu X, Zheng Z. Comprehensive analysis of histone modification-associated genes on differential gene expression and prognosis in gastric cancer. *Exp Ther Med* 2019; **18**: 2219-2230 [PMID: 31452712 DOI: 10.3892/etm.2019.7808]

167 **Yoo C**, Ryu MH, Na YS, Ryoo BY, Lee CW, Kang YK. Vorinostat in combination with capecitabine plus cisplatin as a first-line chemotherapy for patients with metastatic or unresectable gastric cancer: phase II study and biomarker analysis. *Br J Cancer* 2016; **114**: 1185-1190 [PMID: 27172248 DOI: 10.1038/bjc.2016.125]

168 **Yoo C**, Ryu MH, Na YS, Ryoo BY, Lee CW, Maeng J, Kim SY, Koo DH, Park I, Kang YK. Phase I and pharmacodynamic study of vorinostat combined with capecitabine and cisplatin as first-line chemotherapy in advanced gastric cancer. *Invest New Drugs* 2014; **32**: 271-278 [PMID: 23712440 DOI: 10.1007/s10637-013-9983-2]

169 **Schneider BJ**, Shah MA, Klute K, Ocean A, Popa E, Altorki N, Lieberman M, Schreiner A, Yantiss R, Christos PJ, Palmer R, You D, Viale A, Kermani P, Scandura JM. Phase I Study of Epigenetic Priming with Azacitidine Prior to Standard Neoadjuvant Chemotherapy for Patients with Resectable Gastric and Esophageal Adenocarcinoma: Evidence of Tumor Hypomethylation as an Indicator of Major Histopathologic Response. *Clin Cancer Res* 2017; **23**: 2673-2680 [PMID: 27836862 DOI: 10.1158/1078-0432.CCR-16-1896]

170 **Hu W**, Zhang L, Li MX, Shen J, Liu XD, Xiao ZG, Wu DL, Ho IHT, Wu JCY, Cheung CKY, Zhang YC, Lau AHY, Ashktorab H, Smoot DT, Fang EF, Chan MTV, Gin T, Gong W, Wu WKK, Cho CH. Vitamin D3 activates the autolysosomal degradation function against Helicobacter pylori through the PDIA3 receptor in gastric epithelial cells. *Autophagy* 2019; **15**: 707-725 [PMID: 30612517 DOI: 10.1080/15548627.2018.1557835]

171 **Ha J**, Lee JM, Lim Y, Kim MK, Kwon HS, Song KH, Jeon HM, Kang MI, Baek KH. Effect of bisphosphonate on the prevention of bone loss in patients with gastric cancer after gastrectomy: A randomized controlled trial. *Bone* 2020; **130**: 115138 [PMID: 31706052 DOI: 10.1016/j.bone.2019.115138]

172 **Seah KS**, Loh JY, Nguyen TTT, Tan HL, Hutchinson PE, Lim KK, Dymock BW, Long YC, Lee EJD, Shen HM, Chen ES. SAHA and cisplatin sensitize gastric cancer cells to doxorubicin by induction of DNA damage, apoptosis and perturbation of AMPK-mTOR signalling. *Exp Cell Res* 2018; **370**: 283-291 [PMID: 29959912 DOI: 10.1016/j.yexcr.2018.06.029]

173 **Xiong K**, Zhang H, Du Y, Tian J, Ding S. Identification of HDAC9 as a viable therapeutic target for the treatment of gastric cancer. *Exp Mol Med* 2019; **51**: 1-15 [PMID: 31451695 DOI: 10.1038/s12276-019-0301-8]

174 **Regel I**, Merkl L, Friedrich T, Burgermeister E, Zimmermann W, Einwächter H, Herrmann K, Langer R, Röcken C, Hofheinz R, Schmid R, Ebert MP. Pan-histone deacetylase inhibitor panobinostat sensitizes gastric cancer cells to anthracyclines via induction of CITED2. *Gastroenterology* 2012; **143**: 99-109.e10 [PMID: 22465428 DOI: 10.1053/j.gastro.2012.03.035]

175 **Singh A**, Patel P, Jageshwar, Patel VK, Jain DK, Kamal M, Rajak H. The Safety, Efficacy and Therapeutic Potential of Histone Deacetylase Inhibitors with Special Reference to Panobinostat in Gastrointestinal Tumors: A Review of Preclinical and Clinical Studies. *Curr Cancer Drug Targets* 2018; **18**: 720-736 [PMID: 28669336 DOI: 10.2174/1568009617666170630124643]

176 **Kim S**, Kim W, Kim DH, Jang JH, Kim SJ, Park SA, Hahn H, Han BW, Na HK, Chun KS, Choi BY, Surh YJ. Resveratrol suppresses gastric cancer cell proliferation and survival through inhibition of PIM-1 kinase activity. *Arch Biochem Biophys* 2020; **689**: 108413 [PMID: 32473133 DOI: 10.1016/j.abb.2020.108413]

177 **Yang T**, Zhang J, Zhou J, Zhu M, Wang L, Yan L. Resveratrol inhibits Interleukin-6 induced invasion of human gastric cancer cells. *Biomed Pharmacother* 2018; **99**: 766-773 [PMID: 29710474 DOI: 10.1016/j.biopha.2018.01.153]

178 **Barati N**, Momtazi-Borojeni AA, Majeed M, Sahebkar A. Potential therapeutic effects of curcumin in gastric cancer. *J Cell Physiol* 2019; **234**: 2317-2328 [PMID: 30191991 DOI: 10.1002/jcp.27229]

179 **Li W**, Zhou Y, Yang J, Li H, Zhang H, Zheng P. Curcumin induces apoptotic cell death and protective autophagy in human gastric cancer cells. *Oncol Rep* 2017; **37**: 3459-3466 [PMID: 28498433 DOI: 10.3892/or.2017.5637]

180 **Shang HS**, Lu HF, Lee CH, Chiang HS, Chu YL, Chen A, Lin YF, Chung JG. Quercetin induced cell apoptosis and altered gene expression in AGS human gastric cancer cells. *Environ Toxicol* 2018; **33**: 1168-1181 [PMID: 30152185 DOI: 10.1002/tox.22623]

181 **Hemati M**, Haghiralsadat F, Jafary F, Moosavizadeh S, Moradi A. Targeting cell cycle protein in gastric cancer with CDC20siRNA and anticancer drugs (doxorubicin and quercetin) co-loaded cationic PEGylated nanoniosomes. *Int J Nanomedicine* 2019; **14**: 6575-6585 [PMID: 31616144 DOI: 10.2147/IJN.S211844]

182 **Liu C**, Ho PC, Wong FC, Sethi G, Wang LZ, Goh BC. Garcinol: Current status of its anti-oxidative, anti-inflammatory and anti-cancer effects. *Cancer Lett* 2015; **362**: 8-14 [PMID: 25796441 DOI: 10.1016/j.canlet.2015.03.019]

183 **Zheng Y**, Guo C, Zhang X, Wang X, Ma A. Garcinol acts as an antineoplastic agent in human gastric cancer by inhibiting the PI3K/AKT signaling pathway. *Oncol Lett* 2020; **20**: 667-676 [PMID: 32565991 DOI: 10.3892/ol.2020.11585]

184 **Shin H**, Lee YS, Lee YC. Sodium butyrate-induced DAPK-mediated apoptosis in human gastric cancer cells. *Oncol Rep* 2012; **27**: 1111-1115 [PMID: 22160140 DOI: 10.3892/or.2011.1585]

185 **Ke X**, Qin Q, Deng T, Liao Y, Gao SJ. Heterogeneous Responses of Gastric Cancer Cell Lines to Tenovin-6 and Synergistic Effect with Chloroquine. *Cancers (Basel)* 2020; **12** [PMID: 32033497 DOI: 10.3390/cancers12020365]

186 **Huang R**, Jin X, Gao Y, Yuan H, Wang F, Cao X. DZNep inhibits Hif-1α and Wnt signalling molecules to attenuate the proliferation and invasion of BGC-823 gastric cancer cells. *Oncol Lett* 2019; **18**: 4308-4316 [PMID: 31579098 DOI: 10.3892/ol.2019.10769]

187 **Clermont PL**, Fornaro L, Crea F. Elevated expression of a pharmacologic Polycomb signature predicts poor prognosis in gastric and breast cancer. *Epigenomics* 2017; **9**: 1329-1335 [PMID: 28875726 DOI: 10.2217/epi-2017-0074]

188 **Liu S**, Rong G, Li X, Geng L, Zeng Z, Jiang D, Yang J, Wei Y. Diosgenin and GSK126 Produce Synergistic Effects on Epithelial-Mesenchymal Transition in Gastric Cancer Cells by Mediating EZH2 via the Rho/ROCK Signaling Pathway. *Onco Targets Ther* 2020; **13**: 5057-5067 [PMID: 32606728 DOI: 10.2147/OTT.S237474]

189 **Chen YT**, Zhu F, Lin WR, Ying RB, Yang YP, Zeng LH. The novel EZH2 inhibitor, GSK126, suppresses cell migration and angiogenesis via down-regulating VEGF-A. *Cancer Chemother Pharmacol* 2016; **77**: 757-765 [PMID: 26898301 DOI: 10.1007/s00280-016-2990-1]

190 **Zheng YC**, Duan YC, Ma JL, Xu RM, Zi X, Lv WL, Wang MM, Ye XW, Zhu S, Mobley D, Zhu YY, Wang JW, Li JF, Wang ZR, Zhao W, Liu HM. Triazole-dithiocarbamate based selective lysine specific demethylase 1 (LSD1) inactivators inhibit gastric cancer cell growth, invasion, and migration. *J Med Chem* 2013; **56**: 8543-8560 [PMID: 24131029 DOI: 10.1021/jm401002r]

**Footnotes**

**Conflict-of-interest statement:** All authors have no any conflicts of interest.

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**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model**: Single blind

**Peer-review started:** March 21, 2021

**First decision:** May 3, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

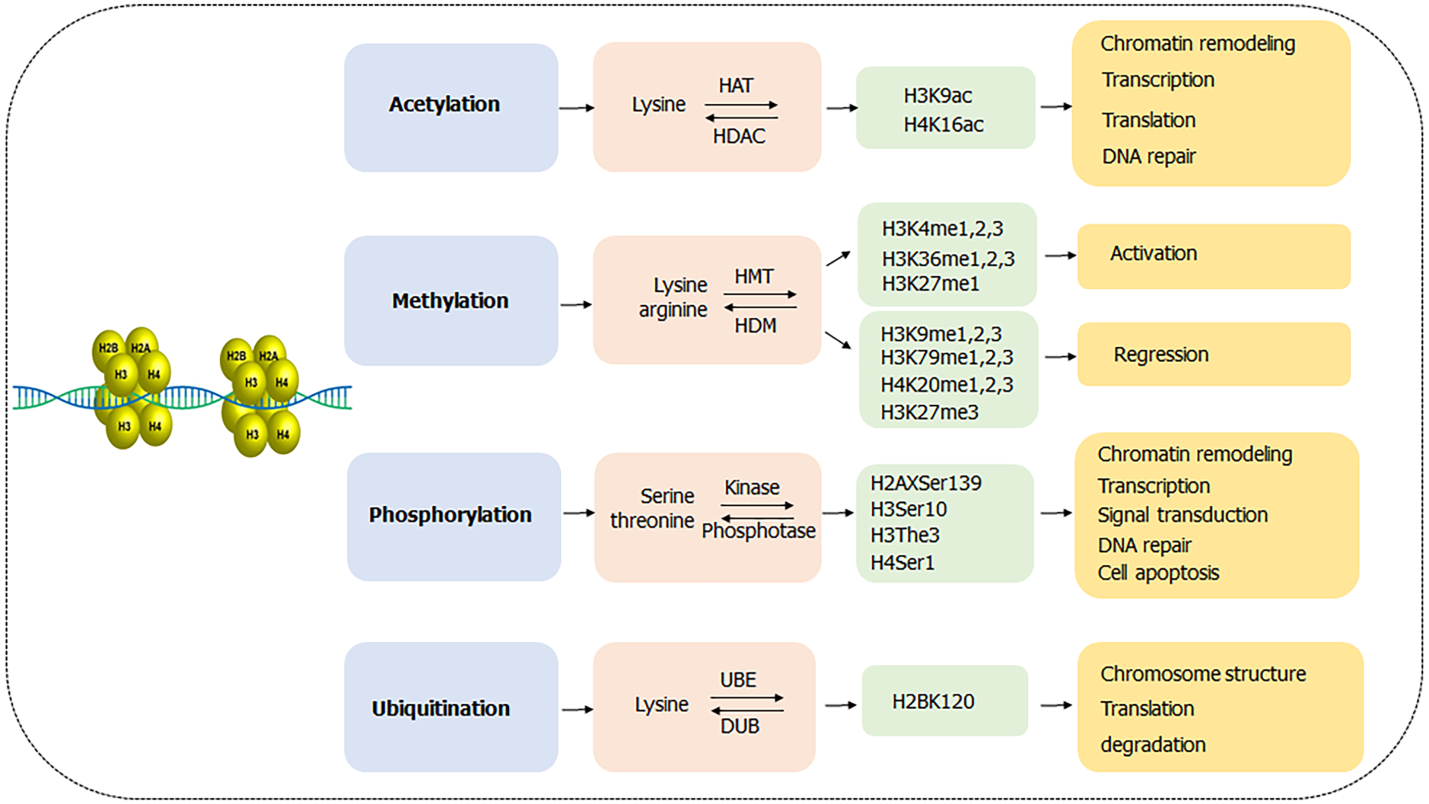
Grade C (Good): C

Grade D (Fair): 0

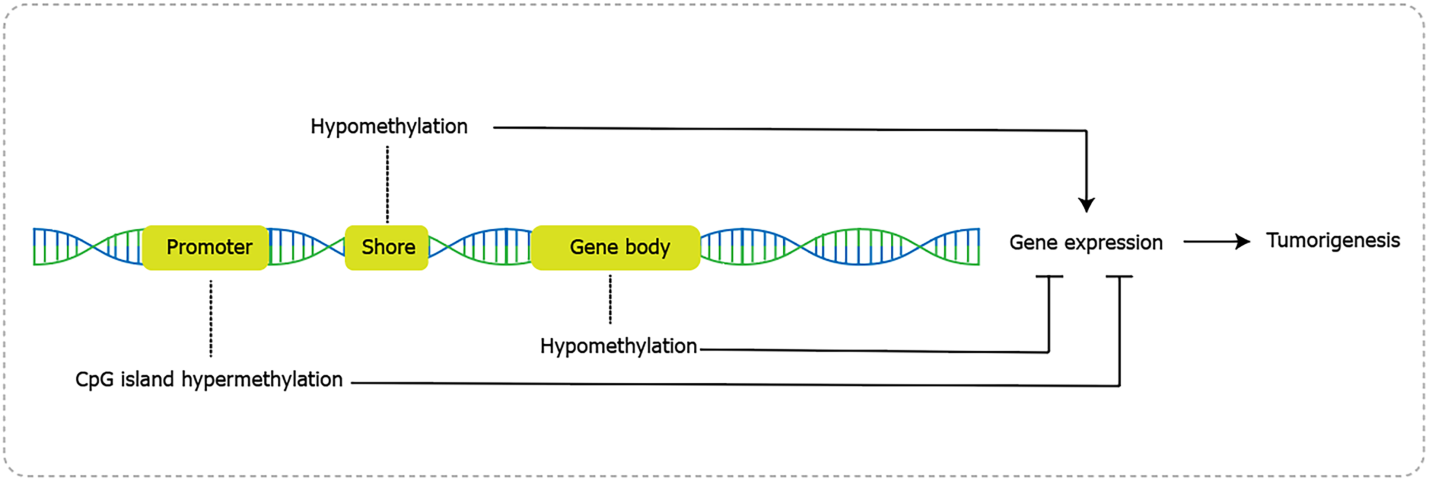
Grade E (Poor): 0

**P-Reviewer:** Burada F **S-Editor:** Ma YJ **L-Editor:** A **P-Editor:** Ma YJ

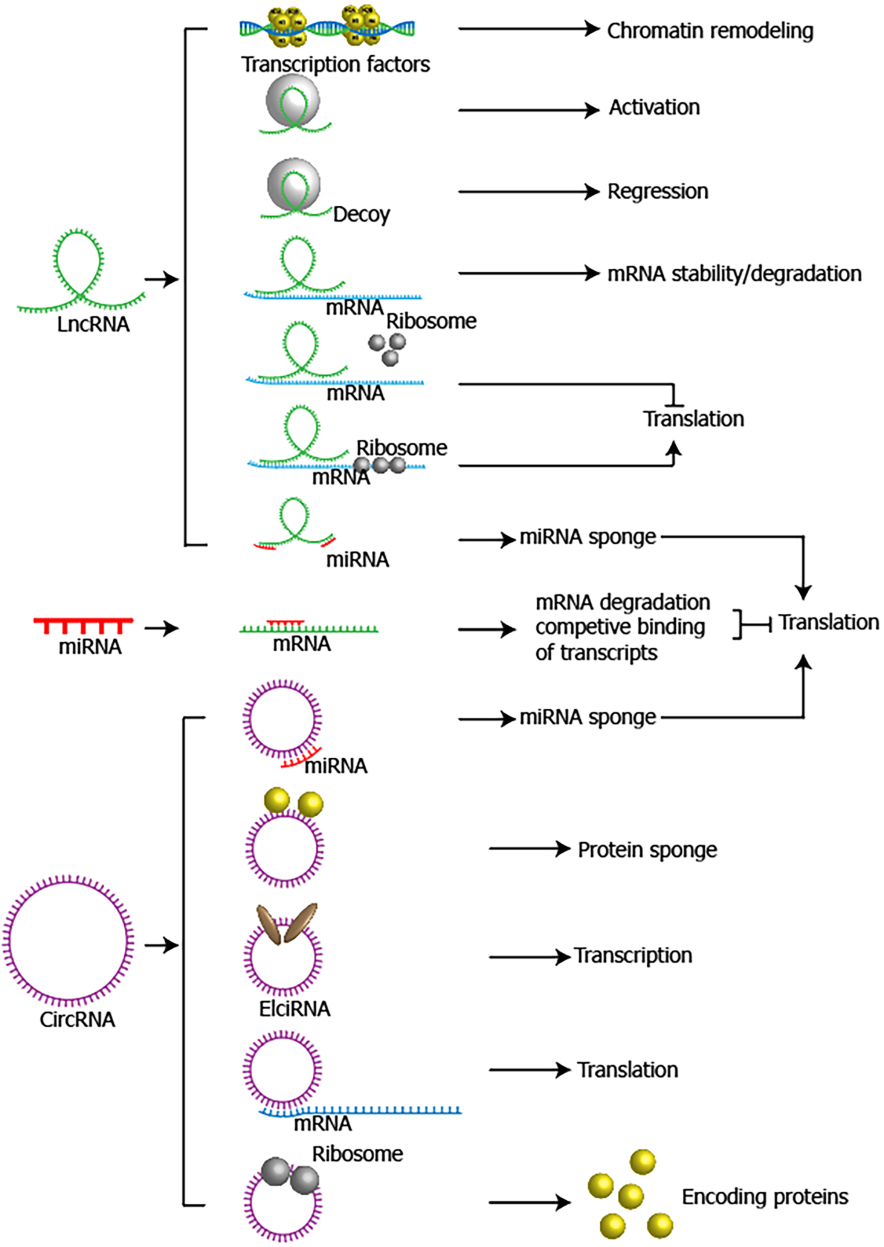
**Figure Legends**

****

**Figure 1 Histone modifications in gastric cancer.** Layers show different histone modifications. Blue panel: modification types; pink panel: modified residues and catalytic enzymes; green panel: epigenetic alterations sites; yellow panel: biological functions regulated by histone modifications. HAT; histone acetylase; HDAC: histone deacetylase; HMT: histone methyltransferase; HDM: histone demethylase; UBE: ubiquitin enzyme; DUB: deubiquitinase.

****

**Figure 2 DNA methylation in** **gastric cancer.** Aberrant methylation in promoter, shore area and gene body altered gene expression and involves in gastric carcinogenesis.

****

**Figure 3 Non coding RNA in gastric cancer.** The major mechanism and biological function of lncRNA, miRNA and circRNA in gastric cancer.

**Table 1 Important miRNAs and their targets and biological functions in gastric cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **miRNAs** | **Expression** | **Targets** | **Functions** | **Ref.** |
| miR-21 | Up | EMT | Tumor growth, metastasis | [89] |
| miR-183 | Up | UVRAG | Cell proliferation, autophagy, apoptosis | [90] |
| miR-765 | Up | BATF2 | Chemosensitivity | [91] |
| miR-155 | Up | TP53INP1 | Cell cycle, proliferation, migration | [92] |
| miR-130b | Up | NFκB, p65 | Cell proliferation, tumorigenesis | [93] |
| miR-92a-1-5p | Up | FOXD1 | Metaplasia | [94] |
| miR-135b | Up | FOXN3/RECK | Cell invasion, CSC-like properties | [95] |
| miR-181a-5p | Up | AKT3 | Cell proliferation, apoptosis, tumor growth | [96] |
| miR-224 | Up | PAK4 | Cell proliferation, migration, | [97] |
| let-7i | Down | COL1A1 | Cell invasion, metastasis | [98] |
| miR-146a | Down | - | Cell migration | [99] |
| MiR-12129 | Down | SIRT1 | Cell cycle, proliferation | [100] |
| miR-27b | Down | NR2F2 | cell proliferation, tumor growth | [101] |
| miR-140-5p | Down | NOTCH1 | Cell proliferation, migration, apoptosis | [102] |
| miR-34a | Down | Snail | Cell proliferation, invasion | [103] |
| miR-9 | Down | TNFAIP8L3 | Cell proliferation, migration | [104] |
| miR-195 | Down | HMGB1 | Chemosensitivity | [105] |

**Table 2 Important lncRNAs and their targets and biological functions in gastric cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **LncRNAs** | **Expression** | **Targets** | | **Functions** | **Ref.** |
| MIAT | Up | | miR-29a-3p/HDAC4 | Cell proliferation, migration and invasion | [106] |
| PANDAR | Up | | CDKN1A | Tumor growth | [107] |
| FOXD2-AS1 | Up | | EphB3 | Tumorigenesis | [108] |
| SMARCC2 | Up | | miR-551b-3p/TMPRSS4 | Cell proliferation, migration | [109] |
| H19 | Up | | miR-519d-p/LDHA | Aerobic glycolysis, proliferation, and immune escape | [110] |
| TINCR | Up | | STAU1/CDKN2B | Cell proliferation, cell cycle | [111] |
| CCAT2 | Up | | E-cadherin, LATS2 | Cell proliferation, invasion | [112] |
| AOC4P | Up | | Vimentin, MMP9 | Cell proliferation, migration, invasion | [113] |
| CTC-497E21.4 | Up | | miR-22-3p/NET1 | Cell cycle, proliferation, invasion | [114] |
| BANCR | Up | | ERK1/2, NF-κB1 | Cell proliferation, apoptosis, chemosensitivity | [115,116] |
| HOTTIP | Up | | miR-216a-5p, miR-615-3p | Chemosensitivity, cell proliferation, apoptosis | [117,118] |
| AC100830.4  CTC-501O10.1  RP11-210K20.5 | Up | | - | Differentially expressed in GC and normal tissue | [119] |
| INHBA-AS1  CEBPA-AS1  AK001058 | Up | | - | Differentially expressed in GC and normal tissue | [120] |
| CYTOP | Up | | miR-103/RAB10 | Cell proliferation, migration, apoptosis | [121] |
| NKX2-1-AS1 | Up | | SERPINE1/VEGFR-2 | Cell proliferation, angiogenesis | [122] |
| NEAT1 | Up | | miR-17-5p/TGFβR2 | Angiogenesis | [123] |
| ZFAS1 | Up | | EPAS1 | Recurrence, metastasis | [124] |
| TSPEAR-AS2 | Up | | EZH2/GJA1, miR-1207-5p/CLDN4 | Tumor progression | [125] |
| TMEM92-AS1 | Up | | YBX1/CCL5 | Tumor progression | [126] |
| CRNDE | Down | | NEDD4-1/PTEN | Chemosensitivity | [127] |
| MEG3 | Down | | miR-181a-5p/ ATP4B | Cell proliferation, migration, apoptosis | [128] |
| PCSK2-2:1 | Down | | - | Differentially expressed in GC and normal tissue | [129] |
| GNAQ-6:1 | Down | | - | Differentially expressed in GC and normal tissue | [130] |
| CTSLP4 | Down | | Hsp90α/HNRNPAB | Cell migration, invasion, EMT | [131] |

**Table 3 Important circRNAs and their targets and biological functions in gastric cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **circRNAs** | **Expression** | **Targets** | **Functions** | **Ref.** |
| circFAM73A | Up | miR-490-3p/ HMGA2 | Cell proliferation, migration, CSC-like properties, chemosensitivity | [132] |
| circAFF2 | Up | miR-6894-5p/ANTXR1 | Cell proliferation, migration, invasion | [133] |
| circHIPK3 | Up | miR-637 /AKT1 | Tumorigenesis | [134] |
| circVAPA | Up | miR-125b-5p/STAT3 | Chemosensitivity | [135] |
| circMAP7D1 | Up | HER2 | Cell proliferation, apoptosis | [136] |
| circ\_0006282 | Up | miR-144-5p/YWHAB | Cell proliferation, metastasis | [137] |
| circ\_0081146 | Up | miR-144/ HMGB1 | Cell growth, migration, invasion | [138] |
| circ\_SMAD4 | Up | miR-1276/ CTNNB1 | Tumorigenesis | [139] |
| circNEK9 | Up | miR-409-3p/MAP7 | Cell proliferation, migration, invasion | [140] |
| circ\_0004104 | Up | miR-539-3p/RNF2 | Cell proliferation, metastasis, glutaminolysis | [141] |
| circPVT1 | Up | miR-152-3p | Chemosensitivity | [142] |
| hsa\_circ\_0023409 | Up | miR-542-3p/ IRS4 | Cell proliferation, metastasis | [143] |
| circ\_0044516 | Up | miR-149-5p/HuR | Cell proliferation, migration, invasion, tumor growth | [144] |
| circLMO7 | Up | miR-30a-3p/ WNT2 | Cell growth, metastasis | [145] |
| hsa\_circ\_0001829 | Up | miR-155-5p/SMAD2 | Cell growth, metastasis | [146] |
| circCUL3 | Up | miR-515-5p/STAT3/HK2 | Cell proliferation, glucose consumption, lactate production, ATP quantity | [147] |
| circTMEM87A | Up | miR-142-5p/ULK1 | Cell proliferation, metastasis | [148] |
| circPTPN22 | Down | EMT | Cell proliferation, migration, EMT, invasion | [149] |
| hsa\_circ\_0004872 | Down | miR-224/Smad4/ADAR1 | Cell proliferation, migration, invasion, tumor growth, metastasis | [150] |
| hsa\_circRNA\_0009172 | Down | miR-485-3p/NTRK3 | Cell proliferation, migration, invasion, tumor growth | [151] |
| circ\_002059 | Down | miR-182/ MTSS1 | Cell proliferation, migration | [152] |
| circ-ITCH | Down | miR-199a-5p/ Klotho | Metastasis | [153] |
| circCUL2 | Down | miR-142-3p/ ROCK2 | Cell transformation, chemosensitivity, tumorigenesis | [154] |

**Table 4 Examples of biomarkers in gastric cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| **Genes** | **Purpose** | **Findings** | **Ref.** |
| *RUNX3* | Diagnosis/prognosis | Methylation status correlates with liver metastasis | [155] |
| *MLH1* | Diagnosis/prognosis | Methylation status correlates with tumor stage | [156] |
| *RASSF1A* | Diagnosis/prognosis | Methylation status correlates with advanced stage, and lymph node positivity | [157] |
| *MGMT* | Diagnosis/prognosis | Methylation status correlates with distant metastasis | [156] |
| *ANOS1* | Diagnosis | Expression correlates with tumor progression | [158] |
| *RPRML* | Prognosis | Expression correlates with survival | [159] |
| *CTD-2510F5.4* | Diagnosis/prognosis | Expression correlates with clinicopathological classification and survival | [160] |
| *lncRNA-GC1* | Diagnosis | Circulating exosomal level correlates with early detection and disease progression | [161] |
| *mesothelin* | Diagnosis | Expression correlates with Peritoneal Recurrence | [162] |
| *MiR-379-5p*  *MiR-410-3p* | Prognosis | Expression correlates with metastasis | [163] |
| *S100A9* | Diagnosis /Prognosis | Expression correlates with tumor aggressiveness | [164] |
| *Notch1/2/3/4* | Prognosis | Expression correlates with immune infiltration | [165] |
| *KAT2A* | Diagnosis | Expression correlates with depth of tumor invasion and tumor stage | [166] |

**Table 5 Examples of epigenetic drugs in gastric cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drugs** | **Targets** | **Status** | **Ref.** |
| Clinical | | | |
| Vorinostat + capecitabine + cisplatin | HDAC | Completed phase II test | [167] |
| Vorinostat + folinic acid+ 5‑fluorouracil+ irinotecan | HDAC | Completed phase I test | [168] |
| Azacytidine + epirubicin/oxaliplatin/capecitabine | DNMT | Completed phase I test | [169] |
| Cholecalciferol + HDACi | HDAC | Induce apoptosis in GC cells;  Prevent bone loss in preliminary trials; | [170,171] |
| Preclinical | | | |
| SAHA | HDAC | Suppress proliferation, induce apoptosis, chemosensitivity in GC cells | [172,173] |
| LBH589 | HDAC | Suppress proliferation, induce chemosensitivity | [174,175] |
| Resveratrol | HAT, HDAC | Suppress proliferation, invasion, tumorigenesis in GC cells | [176,177] |
| Curcumin | HAT, HDAC | Suppress viability, proliferation, migration, induce autophagy, apoptosis in GC cells | [178,179] |
| Quercetin | HAT, HDAC | Induce apoptosis, cell cycle arrest in GC cells | [180,181] |
| Garcinol | HAT, HDAC, SIRTUIN | Suppress oxidation, inflammation, tumorigenesis in GC cells | [182,183] |
| Sodium butyrate | HAT, HDAC | Induce apoptosis in GC cells | [184] |
| Tenovin 6 | SIRTUIN | Induce apoptosis, autophagy in GC cells | [185] |
| DZNEP | HMT | Suppress proliferation, apoptosis, invasion, induce apoptosis in GC cells | [186,187] |
| GSK126 | HMT | Suppress proliferation, cell cycle angiogenesis EMT, tumorigenesis in GC cells | [188,189] |
| Compound 26 | Lysine demethylase | Suppress growth, migration, invasion in GC cells | [190] |